Risk estimation in colorectal cancer surgery

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CHAPTER 1

Introduction & outline of the thesis

SURGICAL TREATMENT OF COLORECTAL CANCER; A HISTORICAL PERSPECTIVE

The Antiquity

Colorectal diseases and its surgical treatment have been described since ancient times. The first written records of colorectal surgery date back to pharaonic Egypt[1]. Probably the most relevant papyrus text with regard to colorectal diseases, is the Chester Beatty Papyrus VI. This text was written around 1,200 BC during the New Kingdom and contains a description of 41 treatments for different anal diseases (pruritus ani, perianal abscess, hemorrhoids and prolapse). In these times, all diseases were thought to arise in the bowel. In a geographic area where intestinal parasitosis was and is very common[2], this philosophy appears to be quite intuitive. Until now, most of the diseases in Egypt still arise in the abdomen (bacterial diarrhea, hepatitis A, typhoid fever and schistosomiasis)[3].

During antiquity, the focus of causative thinking with regard to the development of diseases remained to be the abdomen. One of the famous quote's attributed to Hippocrates; "All disease begins in the gut" nicely illustrates this continuation of ancient Egyptian philosophy. Up to this point, few of the surgical procedures that were performed, were actually documented in detail. This changed during the Roman era. From this period onwards, we have some excellent textbooks and journals on anatomy and surgical procedures. Around 47 AD, "de Medicina" was published by Aulus Cornelius Celsus. De Medicina is a medical treatise that consists of eight books of which the seventh book deals with "the art that cures by the hand". Detailed descriptions are given on the surgical treatment of traumatic bowel injury, perianal fistula, hemorrhoids and fissura.

Middle Ages and Renaissance

During the Middle Ages, the focus of colorectal surgery remained primarily on hemorrhoids, abscesses and fistula (a common disease among knights). Although, in 1376 John of Arderne wrote a very clear treatise on his perspective on rectal cancer. John of Arderne (1307-1392) was a famous English barber surgeon with a special interest in proctology. This treatise contains a clear

description of the clinical presentation, findings of physical examination and prognosis of rectal cancer.

> *"I will first say that the ulceration of it is nothing other than a concealed cancer, that may not in the beginning be recognized by inspection, for it is completely hidden within the anus, and is therefore called bubo for just as bubo (owl) is a beast dwelling in hiding places"*

> *"It is recognized as follows: the doctor should put his finger into the anus of his patient and if he finds within the anus something as hard as stone, sometimes it's just on the side, sometimes on both, so that it hinders the patient from passing excrement, then this is certainly a bubo."*

> *"so that it may never be cured with human treatment, unless it pleases god to help"*

Futhermore, Arderne describes in his treatise the principles of treatment for tumor obstruction (recipes for enema's) and palliative care that are currently still being applied in medical practice.

The Renaissance did not offer many developments with regard to the techniques used in colorectal surgery. However, in this period important advances were made in anatomical knowledge. In "De Humani Corporis Fabrica", the results of Vesalius studies on human anatomy were published. In great detail, the anatomy of the abdomen is being described.

The 18*th* and 19*th* centuries

The increased insight in the anatomy of the abdomen proved to be extremely useful in the 18th century. During this era, many wars were fought (French revolution, Napoleonic Wars, American Revolutionary War). Because of this, battle-field surgeons were able to obtain a lot of experience with the surgical treatment of sharp abdominal injury. Techniques to suture bowel, to create a

fistula or to construct a stoma were developed[4]. In light of these new techniques many attempts were undertaken at surgical bowel resection with the creation of an anastomosis (most with poor result from a patient point of view).

From the beginning of the 19th century, colorectal surgery started to evolve rapidly. At first, the only surgical procedure that was performed for rectal cancer was the creation of a defunctioning stoma. This procedure was promoted largely by Jean Zulema Amussat[5]. Soon attempts at local, perineal, tumor resection were performed. The first "successful" perineal resection was performed by Jaques Lisfranc in 1826. During this period, several techniques were developed for local tumor resection through a perineal (local) approach[6]. These procedures invariably coincided with high perioperative mortality and morbidity. One of the surgeons experimenting with perineal resection was William Ernest Miles. In a series of patients Miles operated on, he observed a 95 percent recurrence rate within 2 years after surgery. Based on postmortem studies in this group he found that local recurrence occurred in the mesocolon and adjacent lymph nodes. He concluded that in order to gain local tumor control, a wide cylindrical resection of the tumor with associated lymph nodes was required. At the same time new techniques were being developed regarding anesthesiology and antisepsis. Because of these developments it became possible to perform a laparotomy and resect proximal tumors under relatively safe circumstances. In 1879 Carl Gussenbauer introduced a procedure for proximal rectal tumors which the distal rectum was left closed in the abdomen and a colostomy was constructed after resection of the tumor[7]. Later on this procedure was propagated by the French surgeon Henri Hartmann and became known as the so called Hartmann procedure.

The 20*th* century and onwards

Miles combined the transabdominal resection method with his insights in tumor spread and recurrence and developed a technique in which the tumor is resected through a combined transabdominal and perineal approach. The abdominoperineal resection (APR) was created. Because of the combined approach it was possible to resect more proximally situated tumors and gain a larger resection margin. Furthermore, the technique allows for a proximal lymph

node dissection. With the introduction of this method, a drastic decrease in local recurrence was achieved (from approximately 100% to 29.5%)[8]. Although an enormous improvement in recurrence rate was obtained, the procedure related mortality remained high (around 30%)[7].

After its introduction by Miles in 1908, the APR remained to be the gold standard for both low and upper rectal cancers during the first part of the 20th century. In this period new insights were gained with regard to tumor spread. Studies done by Cuthbert Dukes (known for the Dukes classification for colorectal cancer) and John Goligher demonstrated that lymphatic tumor spread rarely occurred distal to the primary tumor[9]. This indicated that "below" the primary tumor a smaller resection margin could safely be accepted. The previously accepted distal resection shifted from a 5 cm margin to a minimum of 2 cm margin.

In the past, several techniques had been described to excise the primary tumor and create a primary anastomosis (1888 Hochenegg; Durchzug procedure, 1910 Donald Balfour; anterior resection). None of these became generally accepted because of high mortality rates. However, improved surgical techniques in combination with the acceptance of a smaller distal resection margin led to improved results of sphincter preservation through anterior resection. In 1948, Claude Dixon published his results on sphincter preserving treatment of upper rectal cancer[10]. In this study of 400 patients he observed a perioperative mortality rate of 2.6% and a 5 year survival rate of 64%. Because of these favorable results, sphincter preservation for cancers of the upper rectum became a generally accepted treatment option.

During the early 20th century an important technical development took place that simplified the creation of a "low" anastomosis and increased its safety. After its development by the Russians, the surgical stapling device evolved from a 4kg impractical instrument to a widely available and reliable surgical instrument. In 1973 the first circular stapler was created by the United States Surgical Corporation. The commercially available disposable stapler was launched by Ethicon (Johnson & Johnson) in 1981[1]. Creating a "low" anastomosis was no

longer an extremely difficult and dangerous procedure executed with success only by the technically most gifted surgeons. Because of this development, it became technically possible to do a low anterior resection and create a low anastomosis with acceptable perioperative risks. Because of this development, relatively more patients were eligible for low anterior resection instead of the previous golden standard; the APR.

The next leap in colorectal surgery was based on surgical technique. At the beginning of the 20th century, tumor growth and spread was thought of as a cylindrical process. In this process the tumor would grow in all directions equally. As mentioned before, in the early 20th century, Dukes demonstrated that this conceptual thinking of tumor growth, did not correspond with his examinations of resected specimens. Tumor growth and spread appeared to be laterally confined and spread throughout the lymph nodes mainly occurred in a proximal direction. In 1982, the "total mesorectal excision" (TME) was introduced by Professor Bill Heald at the UK's Basingstoke District Hospital [11]. Heald recognized that both the rectum and mesorectum are embryological derived from the hindgut and can be resected as a single unit by using the relatively avascular plane between the mesorectum and the presacral fascia (Heald's "holy plane"). Using this plane proved to reduce blood loss, reduce lateral positive margins and preserve hypogastric nerves [11-13]. Up to today, the TME technique remains to be the worldwide gold standard for surgical resection of rectal cancer.

During the period when TME was introduced there was another major technical innovation in surgery namely the development and introduction of laparoscopic surgery. The application of laparoscopic techniques in colorectal surgery started relatively slow. Partly this was due to the specific laparoscopic instruments that were needed to perform laparoscopic bowel resections (development of for example Endo-GIA and endoscopic vessel sealing devices). Perhaps a contributing factor was reluctance of the colorectal surgeons to adapt to "new" laparoscopic techniques. Colorectal surgery was largely performed by senior surgeons using manual skills that were acquired over years of training. At first laparoscopic colorectal surgery consisted mostly of laparoscopic

mobilization of the bowel. The actual resection itself was performed outside the bowel through a small laparotomy. The first laparoscopic assisted colon resection was described by Jacobs in 1991[14]. Soon true laparoscopic sigmoid and rectum resections were also being described[15]. The main advantage of laparoscopic techniques appears to be an enhanced postoperative recovery. Disease free survival and overall survival appear to be the same compared to open procedures for rectal cancer[16].

Although TME offers a standardized resection method with improved outcome parameters, surgery alone is not a suitable option for all patients with rectal cancer. Locally advanced tumors that extend outside the mesorectum are technically not suitable for a TME. Furthermore, despite of its many advantages, TME alone coincides with recurrence rates of around 4%[17]. Because of these aspects, multimodality treatment strategies were developed in order to improve local disease control and increase the population of patients eligible for curative resection. The foundations for these strategies were laid out by the Swedish. In their rectal cancer trial[18], patients that were treated with short course radiotherapy prior to TME were compared with patients that were treated with TME alone. In this study, improved local control and an increased long-term survival were observed among the group of patients who received radiotherapy before TME [18,19]. These favorable results of pre-operative radiotherapy were confirmed by the Dutch rectal cancer trial [20]. The multimodality treatment strategies were further extended by adding chemotherapy to the protocol. After several successful cohort studies on neoadjuvant chemoradiotherapy (nCRT), the German rectal cancer trial was executed [21]. This study demonstrated that preoperative conventionally fractionated radiotherapy and concurrent fluorouracil, improved local control in patients with T3, T4 or lymph node positive rectal cancer. Since then, many studies have confirmed improved local control and tumor down staging after nCRT for locally advanced rectal cancer [22-24].

THE INTRODUCTION OF CONSERVATIVE TREATMENT STRATEGIES

Current nCRT protocols have demonstrated impressive pathologic complete response (pCR) rates ranging between 14 and 25% [22,24,25]. Among the patients with a pCR, five year survival appears to be improved and local recurrence is rarely encountered [26]. Based on these studies it was concluded that a significant proportion of patients underwent a major surgical procedure whilst in the resected specimen there were no vital residual tumour cells detectable. It was hypothesized that in these patients, TME could be avoided and instead a watchful waiting approach could safely be employed. Off course a prerequisite for such a strategy is the availability of a careful follow-up protocol for the detection of local recurrence. The first studies on a watchful waiting approach were executed in Sao Paulo, Brazil under the guidance of professor Habr-Gama[27]. In the beginning, the watchful wait strategy was met with skepticism. However, in the past decades several studies from different research groups started to emerge that reported similar beneficiary results of the watchful waiting strategy. Most of these studies report low rates of local recurrence and distant manifestation of disease after watchful waiting [26,28-31].

Apart from a total omission of surgical treatment through a watchful wait strategy, it has also become possible to perform a local excision through Transanal Endoscopic Microsurgery (TEM). This technique has been described for patients with early rectal cancer and patients estimated to have a complete response to nCRT. Several studies have described low surgical morbidity, good functional outcome and low local recurrence rates using the TEM technique in selected patients with low rectal cancer[32-35].

Detection and treatment of recurrent disease

Despite of all modern local and systemic treatment options a significant percentage of patients treated for colorectal cancer with curative intent will develop recurrent disease. Although most of these patients will die from this, a relatively small group of patients with either local recurrent disease or limited metastatic disease to liver or lung may be treated successfully with additional surgery. Most of disease recurrences are encountered during the first 5 years

post initial curative intent surgery. Therefore, most guidelines advocate post treatment surveillance during this period. The purpose of this surveillance is to early identify recurrent disease that can be cured by surgical intervention, and to screen for a potential second primary cancer or pre-cancerous adenomatous polyps. For this purpose, a wide variety of surveillance strategies have been described[36]. Most of these strategies include the use of tumour markers to detect recurrent disease during follow-up.

For colorectal cancer several tumor markers have been identified. The most commonly known and used marker in clinical practice is carcinoembryonic antigen (CEA). This test has been described extensively with regard to its value during follow-up after treatment for colorectal carcinoma [37-40]. Most guidelines advocate the use of serum CEA testing during the first three years after surgical resection making CEA testing an established part of standard follow-up[41,42]. Although many patients with recurrent disease have elevated levels of CEA, not all cases can be detected by looking at CEA values alone [43-45]. Further improvement of detection of recurrent disease might be through determination of additional serum tumor markers during follow-up.

The current era of personalized medicine

The last decades personalized medicine has become more and more important. Treatments are being tailored to an individual patient's needs and wishes. In order to do this, it is necessary to have individualized information on prognosis. This can be done based on a single variable like for example a certain biomarker or complex models using a variety of parameters. Clinical prediction models attempt to estimate the probability of a certain future (clinical) event based on a set of baseline health state related parameters. Apart from predicting events, these models also provide insight in the relative impact of individual predictors and their interaction. In case of colorectal cancer, the potential gain of treatment is high; increased survival and curation of disease. However, the potential harm is also significant; short term perioperative risks on anastomotic leakage or even death and long term risks on decreased quality of life due to presence of a stoma or anorectal dysfunction.

In order to advise patients and make well balanced treatment decisions, it is important to have individualized information with regard to the probabilities on potential harm and benefit. Like in many other fields of surgery, the last decades several field specific risk prediction models have been developed for this purpose [46-49]. Most of the colorectal prediction models contain a significant large number of parameters that are not always readily available in clinical practice and are quite elaborate to calculate.

THESIS OUTLINE

The focus of this thesis rests on methods and models that can aid in clinical decision making during colorectal cancer treatment. In the next chapters we propose several models and investigate several risk factors that might aid in decision making. The sequence of chapters is composed in order to reflect the general course of colorectal cancer treatment.

Chapter 2, describes the results of a study on the predictive performance of several known and previously unknown pre-treatment predictors of pCR after nCRT for rectal cancer. We attempted to identify subgroups groups with increased probability of pCR that might aid in clinical decision making. This was done in a nationwide population based study. To further aid clinical decision making in patients were a complete response to nCRT is suspected, the relation between pCR and surgical morbidity was investigated. The results of this study are given in **Chapter 3**. In this chapter, we hypothesize, that a good response to nCRT coincides with significant local tissue response/ inflammation which may in turn complicate surgical procedure and healing resulting in an increased surgical morbidity. In **Chapter 4**, the development and external validation of a clinical prediction model for in-hospital mortality after colorectal surgery is described. The model was designed to be discriminative, easy to calculate and based on parameters that are readily available in clinical practice. Furthermore, in this chapter a comparison is made between our model and the CR-POSSUM score; a well-accepted more elaborate risk scoring instrument. **Chapter 5** describes the identification of independent risk factors for postoperative delirium after major colorectal surgery. The population of elderly frail patients that are considered for major colorectal surgery in the

Netherlands is increasing at an unprecedented rate. These patients are at an increased risk for developing postoperative delirium. Clear understanding of risk factors for delirium might help select individuals at increased risk who might benefit from targeted perioperative intervention. After having undergone surgical resection of the tumor, patients enter a post-surgery surveillance program. In the Netherlands, carcinoembryonic antigen testing is an established part of standard follow-up. In **Chapter 6** we investigate the (additional) predictive value of serial tissue polypeptide antigen testing after curative intent resection for detection of recurrence of colorectal malignancy. Finally, **chapter 7** contains a summary and discussion of the most important results of this thesis.

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CHAPTER 2

Pre-treatment identification of patients likely to have pathologic complete response after neoadjuvant chemoradiotherapy for rectal cancer

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ABSTRACT

PURPOSE: In selected patients, a wait-and-see strategy after chemo-radiotherapy for rectal cancer might be feasible provided that the probability of pathologic complete response (pCR) is high. This study aimed to identify clinical parameters associated with pCR. Furthermore, we attempted to identify subgroups groups with increased probability of pCR that might aid in clinical decision making.

METHODS: 6,444 patients that underwent surgical resection of a single primary carcinoma of the rectum after neoadjuvant chemoradiotherapy (nCRT) between January 2009 and December 2016 in the Netherlands were included in the study. Data on the outcome variable, pCR, and potential covariates were retrieved from a nationwide database. The variables included in the analysis were selected based on previous studies and were analyzed using univariate and multivariate logistic regression analysis.

RESULTS: pCR was observed in 1,010 patients (15.7%). Pre-treatment clinical tumour stage and signs of obstruction were independently associated with pCR. Nodal stage and presence of metastatic disease, decreased chances of pCR significantly. The best response rate was observed in patients diagnosed with a non-obstructive, well/moderately differentiated adenocarcinoma of the lower rectum with no clinical apparent nodal or distant metastatic disease (pCR ratio 18.8%). The percentage of patients demonstrating pCR decreased in case of symptoms of pre-treatment obstruction or poorly differentiated tumours (pCR ratio of 11.8% and 6.7%, respectively).

CONCLUSION: This nationwide study confirms several of the previously reported clinical predictors of pCR.

INTRODUCTION

Neoadjuvant chemoradiotherapy (nCRT) preceding surgery for locally advanced rectal carcinoma has beneficiary effects on local control[1-3]. Current conventional fractionation nCRT protocols have demonstrated pathologic complete response (pCR) rates ranging between 14 and 25%[1,3,4]. In turn, pCR has been associated with fewer local recurrences and an improved five year survival[5]. In the past decade, several studies have described the results of patients estimated to have complete clinical response on imaging and proctoscopy after nCRT that were not treated with surgery[6,7]. In selected patients, careful follow-up through endoscopic, clinical, and radiographic evaluation, demonstrated low rates of local recurrence and distant manifestation of disease[5-8]. In addition to a watch and wait approach, low local recurrence rates after local excision alone, in patients estimated to have complete clinical response have been reported[9-12]. In order to select patients that might benefit from these rectal preserving strategies, an accurate estimation should be made whether an individual patient is likely to have pCR.

Unfortunately clinical estimation of complete response is not an accurate predictor of pCR. Digital rectal examination, proctoscopy or examination under anesthesia do not accurately predict tumour response[13]. Several studies have investigated the role of imaging modalities such as transrectal endoscopic ultrasound, magnetic resonance imaging and integrated positron emission tomography. None of these modalities have proven to accurately diagnose pCR[14-17]. Some promising results have been shown for diffusion-weighted MRI[18]. In addition to information on tumour size, diffusion-weighted MRI provides information on tumour function and biology. Despite this, differentiating between areas of fibrosis and tumour remains difficult, resulting in frequent overestimating of residual tumour[19]. Thus the best estimation of true complete response remains full pathologic examination of the resected specimen.

As outlined above, in selected patients a conservative treatment strategy after chemoradiotherapy, might be feasible provided that the risk on local recurrence is low and recurrent disease is detected at an early stage4. Despite of modern

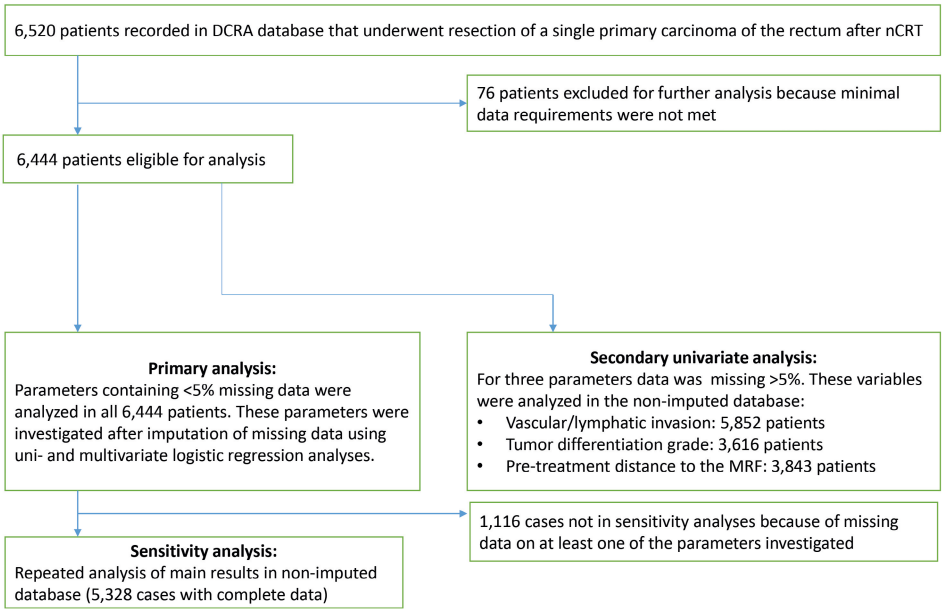
imaging technology, selecting patients likely to have pCR after nCRT remains difficult leading to frequent overestimation of tumour residual. Several studies have described potential predictors for pCR after nCRT. However, most studies address a limited number of parameters in a relatively small and selected population. The aim of this study was to confirm and quantify the association between pCR and several previously identified clinical predictors. Based on the variables that were found to be independently associated with pCR, an attempt was made to identify subgroups with high or low probability on pCR. Since previous studies are based on relatively small and selected patient populations, we chose to investigate a relatively large number of parameters in an unselected nationwide population.

MATERIALS AND METHODS

Population

Data were obtained from the Dutch ColoRectal Audit (DCRA, www.dica.nl/dcra) database. In this database, data are recorded on all patients that have undergone colorectal cancer surgery in the Netherlands. Because participation in the DCRA is made obligatory by the Dutch Health Care Inspectorate, all 92 hospitals performing colorectal cancer surgery in the Netherlands participate in data delivery to this nation wide database. In the DCRA, data are recorded considering 212 parameters including; demographic characteristics, pre-operative work-up, pre-operative clinical staging, procedures performed and results of pathological examination. Between January 2009 and December 2016 a total of 6,520 patients were recorded to have undergone surgical resection of a single primary carcinoma of the rectum after nCRT in the DCRA database. Patients without information on postoperative tumour staging or date of surgery were excluded from the analysis. A total number of 6,444 patients met the minimal data requirements and were found eligible for analysis. In case of a relatively large amount of missing data (>5%) or data missing not at random (MNAR) on a certain parameter, this parameter was not included in the main multivariate analysis. These variables were analyzed using univariate analysis only and reported separately. A schematic representation of the inclusion process is displayed in Figure 1. As this was an observational study, and study data could not be traced back to individual patients, the study received ethical review board exemption status.

Figure 1 Patient inclusion



Definitions

The primary outcome variable was pCR which was defined as the absence of histological evidence of vital tumour cells at the primary tumour site or locoregional lymph nodes in the resected specimen. Mortality was defined as mortality of any cause, in the course of the concerning hospital admission or within 30 days after surgery. Parameters that were considered to be potentially associated with the primary outcome variable pCR were selected based on the results of previously published studies. Variables considered were; distance from the anal verge[20,21] in centimeters measured by endoscopist, tumour size (pretreatment clinical T stage)[22], nodal involvement (pretreatment clinical N stage) [22], metastatic disease (pre-treatment clinical M stage), diabetes mellitus[23,24] (stratified for insulin depended and non-insulin dependent diabetes mellitus), histologic subtype (defined as; adeno-, mucinouscarcinoma), time interval from nCRT to surgery[21,25] and pre-operative anemia[21] (defined as preoperative hemoglobin levels<7mmol/l in male patients and hemoglobin levels<6.5 mmol/l in female patients). In case no data were entered in the database with regard to the presence of anemia, it was assumed to be absent. Pretreatment clinical and post treatment pathological tumour and nodal classification was done

according to the 6th edition of the American Joint Committee on Cancer TNM classification system.

Other covariates that were included in the analysis were; age at time of diagnosis, year of surgery, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, pre-treatment distance to mesorectal fascia (MRF) (defined as < 1mm on MRI), vascular or lymphatic invasion and signs of pre-treatment obstruction (in case no data were entered in the database with regard to the presence of sigs of obstruction, it was assumed to be absent).

Power analysis

Twelve covariates were investigated. Based on a rule of thumb of 10 cases per parameter[26], we estimated to require 120 cases of pCR in our study population. Previous reports from the DCRA database demonstrated that 22% of patients had either AJCC stage III or IV disease. According to current nationwide guidelines (http://www.oncoline.nl/colorectaalcarcinoom), all patients with stage IV disease and a large part of patients with AJCC stage IIIa and IIIb disease should be considered for nCR. Based on an estimated 10% pCR rate, obtaining a population with at least 120 cases of pCR from the DCRA database seemed procurable.

Handling of missing data

Missing value analysis was conducted by performing Little's MCAR test in order to identify potential patterns in missing data that might bias the analysis. In case of a not significant Little's MCAR test, data were considered to be missing completely at random (MCAR) and therefore found to be eligible for multiple imputation. As a second prerequisite for data imputation, variables were only considered for imputation technique when the amount of missing of data was smaller than 5%. Seven parameters met the two above mentioned criteria; BMI (4.2% missing data), distance from the anal verge (3.7% missing data), ASA classification (0.5% missing data), pretreatment clinical T stage (1.8% missing data), pretreatment clinical N stage (2.6% missing data), pre-treatment clinical M stage (2.6% missing data) and histologic subtype (2.3% missing data). For

these variables, Little's MCAR test was not significant (Chi-Square = 0.862, DF =2, Sig.=0.650). For these parameters the data were concluded to be MCAR and therefore multiple missing value imputation technique was considered safe and was applied.

Statistical analysis

Patient and disease characteristics were investigated and reported. Univariate logistic regression analyses were performed to identify variables associated with the primary outcome variable; pCR. Continuous variables were categorized into clinical relevant subgroups. This way, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. After univariate analysis, multiple logistic regression analyses were performed to identify variables that were independently associated with pCR. Parameters with a P-value under 0.250 in univariate analysis were entered in the model using a backward stepwise approach[27]. The robustness of our findings was tested by conducting a sensitivity analysis. This was done by repeating the analysis of our main results on the non-imputed database using only complete cases (cases containing no missing data on the concerning parameters). Three variables did not meet the criteria for data imputation; vascular or lymphatic invasion (9,2% missing data), tumour differentiation grade (43.9% missing data) and pre-treatment distance to the MRF (40.4% missing data). In a secondary analysis, these variables were analyzed using univariate analysis only. For this analysis the original, non-imputed database was used. Based on the potential risk estimators that were identified and quantified we attempted to identify subgroups with either high or low risk on pCR. P-values under 0.05 were considered to be statistically significant. All calculations were performed using the Statistical Package for the Social Sciences (SPSS) version 23 (Chicago, IL, USA).

RESULTS

A total of 6,444 patients met the inclusion criteria and were selected from the DCRA database. The patient characteristics of this population are summarized in Table 1.

Table 1 Patient and disease characteristics

	Number of patients N=6,444	%
Gender		
Male	4.113	63.8
Female	2.331	36.2
Age		
<50	563	8.7
50-60	1359	21.1
60-70	2486	38.6
70-80	1771	27.5
>80	263	4.1
ASA classification		
1	1742	27.0
2	3928	61.0
3	724	11.2
4	19	0.3
Missing data	31	0.0
Diabetes Mellitus		
No	5663	87.9
Yes	781	12.1
pre-operative anemia		
No	5683	88.2
Yes	761	11.8
BMI		
<20	351	5.4
20-25	2354	36.5
25-35	3267	50.7
>35	200	3.1
Missing data	272	4.2
Pre-operative signs of obstruction		
No	6162	95.6
Yes	282	4.4
Distance to the anal verge (cm)		
Low (0-6)	3424	53.1
Mid (7-11)	2033	31.5
High (≥12)	750	11.6
Missing	237	3.7
Clinical T stage		
cT1	44	0.7
cT2	494	7.7
cT3	4443	68.9
cT4	1208	18.7
Missing data	255	3.9

Table 1 Continued

	Number of patients N=6,444	%
Clinical N stage		
cN0	1104	17.1
cN1	2262	35.1
cN2	2646	41.1
Missing data	169	2.6
Clinical M stage		
M0	5371	83.3
M1	467	7.2
Missing data	168	2.6
Year surgery		
2009-2010	1114	17.3
2011-2012	1810	28.1
2013-2014	1943	30.2
2015-2016	1577	24.5
Procedure		
Anterior resection	3640	56.5
Abdominoperineal resection	2627	40.8
Missing data/ not specified	177	2.7
Histologic subtype		
Adenocarcinoma	5840	90.6
Mucinouscarcinoma	287	4.5
Other/ non-specified	166	4.9

ASA: American Society of Anesthesiologists; BMI: Body Mass Index

Median age was 65 years (range 18–93). All patients were operated on electively for a primary malignancy of the rectum. In most cases the tumour was an adenocarcinoma (90.6%). Procedures performed consisted mostly of either an anterior resection (56.5%) or an abdominoperineal resection (40.8%). In a small percentage of cases (0.7%), the exact procedure was not specified. After the large majority of procedures performed, no cancerous cells were seen in the circumferential resection margins of the resected specimen (5967, 92.6%).

The presence of our primary outcome variable pCR, was observed in 1010 patients (15.7%). During the study period, the percentage of patients observed to have pCR increased gradually from 13.5% in 2009 and 2010 up to 16.8% in 2015 and 2016. Partial response (downgrading of TNM stage) was observed in

3837 patients (59.5%). Reported mortality was 1.2% (n=75). During the study period, the number of patients treated with nCRT and subsequent surgery for rectal carcinoma increased over the years (17.3% of the included patients were treated in 2009 and 2010 compared to 24.5% of the included patients treated in 2015 and 2016).

Analysis *excluding* vascular or lymphatic invasion, tumour differentiation grade and pre-treatment distance to the MRF

Parameters that were associated with pCR in univariate analysis were pre-operative anemia (presence of anemia increased the probability of pCR: OR 1.35; 95% CI 1.11-1.64), pre-treatment signs of obstruction (signs of obstruction decreased the probability of pCR: OR 0.53; 95% CI 0.36-0.81), pre-treatment clinical M stage (patients with metastatic disease demonstrated a decreased probability for pCR: OR 0.35; 95% CI 0.24-0.50) and histologic subtype (patients with a mucinous carcinoma demonstrated a decreased probability for pCR compared to adenocarcinoma: OR 0.56; 95% CI 0.36-0.85). Table 2 summarizes the unadjusted odds ratios of the variables that were tested.

Table 2 Results of univariate analysis (N=6,444)

Parameter	OR (95% CI)	p-value
ASA classification		0.10
1	1	
2	0.90 (0.78 – 1.05)	0.19
3	0.73 (0.57 – 0.94)	0.02
4	0.60 (0.15 – 2.46)	0.46
Diabetes mellitus		0.29
No	1	
NIDDM	1.02 (0.81 – 1.29)	0.86
I DDM	0.71 (0.46 – 1.11)	0.14
pre-operative anemia		
No	1	
Yes	1.35 (1.11 – 1.64)	0.002
Pre-treatment signs of obstruction		
No	1	
Yes	0.53 (0.36 – 0.81)	0.003

Table 2 Continued

Parameter	OR (95% CI)	p-value
Distance to the anal verge (cm)		0.13
Low (0-6)	1	
Mid (7-11)	0.90 (0.78 – 1.05)	0.17
High (≥12)	0.82 (0.66- 1.03)	0.08
Clinical T stage		0.15
cT1	1	
cT2	0.78 (0.39 – 1.55)	0.48
cT3	0.71 (0.37 – 1.36)	0.30
cT4	0.45 (0.23 – 0.88)	0.02
Clinical N stage		0.05
cN0	1	
cN1	1.08 (0.88 – 1.32)	0.31
cN2	0.90 (0.74 – 1.09)	0.20
Clinical M stage		
M0	1	
M1	0.35 (0.24 – 0.50)	0.000
Year surgery		0.08
2009 - 2010	1	
2011 - 2012	1.16 (0.94 – 1.44)	0.17
2013 - 2014	1.30 (1.05 – 1.60)	0.02
2015 – 2016	1.25 (1.01 – 1.56)	0.04
Procedure		
Anterior resection	1	
Abdominoperineal resection	1.08 (0.94 – 1.24)	0.27
Histologic subtype		
Adenocarcinoma	1	
Mucinous carcinoma	0.56 (0.36 – 0.85)	0.006
Interval nCRT to surgery (weeks)		0.12
1 – 8	1	
9 – 16	2.18 (0.67 – 7.12)	0.19
17 – 24	2.26 (0.71 – 7.18)	0.16
>24	2.07 (0.64 – 6.68)	0.22

OR: odds ratio; CI: confidence interval; ASA: American Society of Anesthesiologists

Variables that were not significant in univariate analysis but were eligible (overall p-value < 0.25) for multivariate analysis were; pretreatment clinical N stage (patients pre-operatively staged as N2 demonstrated a decreased probability for pCR compared to patients staged N0 and N1: OR 0.90; 95% CI 0.74-1.09), distance to the anal verge (closer proximity to the anal verge

was associated with higher probability of pCR), year of surgery (during the study period the probability of pCR increased gradually), ASA classification (higher ASA classification was associated with decreased probability of pCR), clinical T stage and interval nCRT to surgery (an increased time interval from nCRT to surgery was associated with a higher pCR ratio). A total number of 11 parameters were thus found eligible for multivariate analysis. The results of the multivariate analysis are demonstrated in Table 3.

Table 3 Results of multivariate analysis (N=6,444)

Parameter	OR (95% CI)	p-value
pre-operative anemia		
No	1	
Yes	1.28 (1.04 – 1.57)	0.019
Pre-treatment signs of obstruction		
No	1	
Yes	0.61 (0.40 – 0.94)	0.024
Clinical T stage		0.23
cT1	1	
cT2	0.79 (0.36 – 1.71)	0.54
cT3	0.73 (0.35 – 1.54)	0.41
cT4	0.54 (0.25 – 1.16)	0.11
Clinical N stage		0.28
cN0	1	
cN1	0.91 (0.74 – 1.13)	0.39
cN2	0.77 (0.48 – 1.23)	0.27
Clinical M stage		
M0	1	
M1	0.35 (0.24 – 0.52)	0.00
Year surgery		
2009 - 2010	1	
2011 - 2012	1.21 (0.96 – 1.52)	0.12
2013 - 2014	1.39 (1.11 – 1.75)	0.01
2015 – 2016	1.46 (1.15 – 1.85)	0.00
Histologic subtype		
Adenocarcinoma	1	
Mucinouscarcinoma	0.57 (0.38 – 0.88)	0.01

OR: odds ratio; CI: confidence interval;

Variables independently associated with pCR were; pre-operative anemia (anemic patients were more likely to have pCR: OR 1.28; 95% CI 1.04-1.57), pre-treatment signs of obstruction (patients with signs of obstruction were less

likely to have pCR: OR 0.61; 95% CI 0.40-0.94), clinical M-stage (patients with metastatic disease were less likely to have pCR: OR 0.35; 95% CI 0.24-0.52), year of surgery (2009-2010 versus 2015-2016: OR 1.46; 95% CI 1.15-1.85) and histologic subtype (patients with a mucinous carcinoma demonstrated a decreased probability for pCR compared to adenocarcinoma: OR 0.57; 95% CI 0.38-0.88). Tumour and nodal stage were included in the logistic regression model. However, the overall p-values of the corresponding regression coefficients did not prove to be significant in multivariate analysis.

Sensitivity analysis: Repeating multivariate analysis in the non-imputed database using exclusively cases with complete data (5,328 cases, 82.7%), yielded comparable results.

Univariate analysis of vascular or lymphatic invasion, tumour differentiation grade and pre-treatment distance to the MRF

Table 4 summarizes the unadjusted odds ratios of the variables that were tested in this way.

Table 4 Results of univariate analysis on complete cases of variables MNAR/ large amount of missing data

Parameter	OR (95% CI)	p-value
Vascular/ lymphatic invasion		
No	1	
Yes	0.15 (0.10 – 0.23)	0.00
Tumour differentiation grade		
Well/ moderate	1	
Poor	0.44 (0.24 – 0.79)	0.01
Distance to MRF		
≥ 1mm on MRI	1	
< 1mm on MRI	1.06 (0.89 – 1.27)	0.90

MNAR: missing not at random; OR: odds ratio; CI: confidence interval; MRF: mesorectal fascia

Vascular or lymphatic invasion was associated with pCR (presence of invasiveness decreased probability of pCR: OR 0.15; 95% CI 0.10-0.23). Tumour differentiation was also found to be associated with pCR (poorly differentiated tumours demonstrated decreased probability of pCR: OR 0.44; 95% CI 0.24 -

0.79). In contrast to these parameters, pre-treatment distance to the MRF could not be associated with pCR (OR: 1.06; 95% CI 0.89-1.27).

Subgroups with either high or low risk on pCR

An improved response rate was observed in a subgroup of 444 patients (6.8%) diagnosed with a non-obstructive well/moderately differentiated adenocarcinoma of the lower rectum with no clinical apparent nodal or distant metastatic disease (84 patients with pCR, 18.9%). The percentage of patients demonstrating pathologic complete response increased when surgical treatment was performed between 16 and 24 weeks post nCRT (33 out of 149 patients with pCR, ratio 22%). In the subgroup of patients with a non-obstructive well/moderately differentiated adenocarcinoma (n=5675, 88.1%) the presence of nodal involvement had little effect on pCR ratio whilst the presence of distant metastatic disease or poor tumour differentiation grade drastically decreased pCR ratio (pCR ratio of 8.3% and 6.7% respectively; decrease 10.5% and 12.1%, respectively).

Lowest pCR rates were observed in patients with relatively large tumours. Patients with a non-obstructive tumour large (T4) adenocarcinoma demonstrated an overall response ratio of 11.4% (115 out of 1012 patients). This ratio decreased to 7.9% in case of pre-treatment symptoms/signs of obstruction (8 patients with pCR out of 110). Patients with tumour stage 4 adenocarcinoma without signs of obstruction appeared to do worse in case of nodal involvement (pCR ratio in T4N2M0 patients: 8.7%). Adding the presence of distant metastatic disease worsened the pCR ratio further to 5.1% (4 patients with pCR out of 78). The lowest pCR ratio was observed for patients with large, poorly differentiated tumours (T4N2M0/1 poorly differentiated, pCR ratio 2.4%).

DISCUSSION

In the present study, the association between a set of parameters and pCR after nCRT for rectal cancer was investigated in a nationwide unselected cohort. Variables that were being analyzed were selected, based on previously published smaller cohort studies. In accordance with these studies, we confirmed that a

larger tumour size is associated with a decreased pCR rate. Both, pre-treatment clinical tumour stage and signs of obstruction (as a proxy for tumour size) were found to be associated with pCR (Tables 2 and 3). Apart from pre-treatment tumour stage, nodal stage (especially patients who were pre-treatment staged as having at least 4 positive nodes) and presence of metastatic disease, decreased chances of pCR significantly. Furthermore, pCR was confirmed to be related to histologic subtype (in favor of adenocarcinoma), distance to the anal verge, ASA classification (in favor of the lower ASA subgroups) and year of surgery (patients treated at the end of the study period demonstrated higher probability of pCR). There were no significant differences in age, gender, BMI, diabetes mellitus, distance to the MRF on MRI (<1mm) and type of procedure performed.

The overall pCR rate was 15.7%. Despite of the potential predictors that were confirmed and identified, we were not able to define subgroups with a probability on pCR higher than 21%. The high and low risk groups that were identified consisted of relatively small proportions of the study population. For these reasons, accurate prediction of pCR solely based on the pre-treatment clinical parameters appeared to difficult and insufficient to guide clinical decision making. Unfortunately the concerning surgical procedures for rectal cancer (anterior and abdominoperineal resection) are associated with significant morbidity and mortality. In some sub populations procedure related risks are higher. For example older age has been associated with a higher 1-year overall, cancer-specific, and cardiovascular-specific mortality[28]. Furthermore, older frail patients are at increased risk of postoperative complications and mortality[29]. Especially in this group of frail elderly patients, exposed to an increased risks on procedure related complications, a careful consideration should be made between potential harm and benefit of the treatment options. In order to make a well balanced treatment decision for these patients, knowledge and consideration of predictors for pCR appears valuable.

As mentioned before, one of the variables associated with pCR was the year of surgery. Over the past 8 years response rates gradually improved. Interestingly, during the study period (in the year 2014) a new nationwide guideline for the

treatment of colorectal carcinoma was introduced in the Netherlands (http://www.oncoline.nl/colorectaalcarcinoom). In this new guideline the criteria for pre-treatment nodal status determination on MRI were adjusted. This was done in order to decrease the false positive rate of nodal staging on MRI. Furthermore, in the new guideline, criteria for nCRT were specified more clearly compared to the previous guideline. These two changes might have led to a change in patient selection for nCRT which in turn might have led to higher pCR rates over the past years. Apart from tumour size and nodal status, one of the criteria for nCRT that was added in the 2014 Dutch guideline is distance to the MRF smaller than 1 millimeter on MRI. Unfortunately this parameter was poorly documented in the database (40.4% missing data), and its impact on pCR rate could therefore not be assessed reliably. However, our results suggest that a distance to MRF smaller than 1 millimeter on MRI does not influence the probability on pCR. We did not investigate the relation between distance to MRF on MRI and achieving a resection with tumour free margins. Therefore we are unable to make any recommendations with regard to its current incorporation as a criteria for nCRT in the guideline.

Most parameters that were associated with pCR in our study were also linked to pCR in other studies. Tumour size (pre-treatment tumour and nodal stage)[22,30,31], distance to the anal verge[20,21], histologic subtype and interval to surgery[21,25]. It seems logical that increased tumour size and poor differentiation grade are related with a decreased probability on pCR. Time interval to surgery seems a somewhat less obvious predictor of pCR. It has been postulated that increasing the interval to surgery allows for ongoing tumour necrosis and therefore improves the pCR rate[32]. Previously published studies reported favorable results of using time intervals over 7-8 weeks[22,32,33]. Based on these results we stratified our time intervals and demonstrated a similar result; the odds ratio on pCR was above 2 for all intervals at least 8 weeks post nCRT. These intervals could not be made significant in multivariate analysis. However, in combination with previously published studies it seems likely that allowing an interval to surgery of at least 7 to 8 weeks increases the pCR rate.

Like previously reported in other studies, tumours located more closely to the anal verge[20,21] were more likely to show pCR. Although also reported in other studies, this relation was found to be relatively small (Table 2) and was not significant in multivariate analysis. In contrast to this finding, other studies have reported no differences in pCR rates related to location[34] or even a higher risk of local recurrence for lower tumours[35]. Altogether, the potential beneficiary effects of tumour location appear to be small and therefore seem to be of little importance as a predictor for pCR. The presence of distant metastatic disease was also considered in our study as a potential predictor of pCR. Like with tumour size, the presence of metastatic disease can be interpreted as an indicator of aggressiveness of the tumour. We therefore find it not surprising that pCR was strongly related to M-stage in multivariate analysis.

Armstrong et al. demonstrated higher hemoglobin levels in patients with pCR in univariate analysis[21]. This relation could not be confirmed in their multivariate analysis. Also a relation between pre-treatment anemia and longer term local control has been demonstrated[36]. It has been postulated that anemia contributes to intra-tumoural hypoxia and tumor resistance to ionizing radiation. However, evidence for this theory is sparse. The relation between anemia and pCR demonstrated in our study seems counterintuitive to this theory and previously published results. In this study a small effect in favor of anemia was detected (OR 1.28) with a confidence interval approaching one (95% CI: 1.04 – 1.57). We cannot offer a molecular based hypothesis that explains this finding. The relation that was demonstrated could consist of a false positive one. Another option, more in line with previously published studies, is that if there is a relation, it is a small one (or none). This seems more likely since, our study appears to confirm most of the previously demonstrated predictors and consists of a large unselected population of patients in which data were prospectively collected.

The present study has a few limitations that should be mentioned. Firstly, although the database that was used consisted of a large amount of unselected nationwide data, it was primarily designed for benchmark purposes. Although many of the previously described predictors were present in the database,

some were poorly documented. Secondly, even though many parameters were documented, several parameters that were previously shown to be predictor of pCR were not present in our database and could therefore not be analyzed (CEA level, the exact nCRT regimen, statin use). Thirdly, it is likely that because of errors during data entry information bias was created. However we find it unlikely that wrongness of data was related to the outcome variable pCR. Since our database is large we expect that this phenomenon has had little influence on our results.

In conclusion, this large nationwide prospective study on predictors of pCR after nCRT for primary carcinoma of the rectum confirms several of the previously reported predictors of pCR. The best response rate was observed in patients diagnosed with a non-obstructive well/moderately differentiated adenocarcinoma of the lower rectum with no clinical apparent nodal or distant metastatic disease. The worst pCR ratio was observed for patients with large poorly differentiated tumours.

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CHAPTER 3

Population-based study of morbidity risk associated with pathological complete response after chemoradiotherapy for rectal cancer

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ABSTRACT

BACKGROUND: Neoadjuvant chemoradiotherapy (nCRT) for locally advanced rectal cancer may induce a pathological complete response (pCR), but may increase surgical morbidity due to radiation-induced fibrosis. In this study the association between pCR and post-operative surgical morbidity was investigated.

METHODS: Patients with rectal cancer that underwent nCRT followed by TME between 2009 and 2017 in the Netherlands were included. Data were stratified into patients that underwent resection with the creation of a primary anastomosis and permanent stoma procedures. The association between pCR and postoperative morbidity was investigated using uni- and multivariable logistic regression analyses.

RESULTS: pCR was observed in 976 (12.2%) of 8.003 patients. In the group of patients with a primary anastomosis (N=3.472), presence of pCR was significantly associated with surgical complications (n=122, 27.5% versus n=598, 19.7% without pCR) and anastomotic leak (n=35, 7.9% versus n=173, 5.7% without pCR). Associations between pCR and surgical complications and pCR and anastomotic leak were also present in multivariable analyses ($OR_{adjusted}$: 1.53, 95% CI: 1.22-1.92; $OR_{adjusted}$: 1.41, 95% CI: 1.03-2.05, respectively). In the permanent stoma group (N=4.531), surgical complications were observed in 120 (22.5%) patients when pCR was present compared to 798 (20%) patients when pCR was not present ($OR_{adjusted}$: 1.17, 95% CI: 0.94-1.46).

CONCLUSION: Patients with pCR in whom an anastomosis was created were at an increased risk for developing anastomotic leak.

INTRODUCTION

In the Netherlands, patients with locally advanced rectal cancer (cT3 with distance to MRF ≤1 mm or cT4, and/or high likelihood of 4 or more positive lymph nodes within the mesorectum or positive lymph nodes outside the mesorectum based on MRI) are treated according to national guidelines (http://www.oncoline.nl/colorectaalcarcinoom, website consulted on 10-10-2018). The mainstay of curative treatment for high risk and locally advanced rectal cancer is neoadjuvant chemoradiotherapy (nCRT) followed by surgical resection according to total mesorectal excision (TME) principles. The majority of patients will undergo a low anterior resection (LAR) with a primary anastomosis. In patients were sphincter preservation is not feasible, an abdominoperineal resection (APR) is performed. In the past years, the wait and see policy in patients with a clinical complete response has gained more acceptance[1-4]. Especially among the elderly and frail patient population this strategy is gaining in popularity when a clinical complete response is encountered.

The relation between tumour response to nCRT and surgical procedure related morbidity is still unclear. Both increased and decreased morbidity have been reported in the literature[5-8]. Horrisberger et al. reported markedly enhanced rates of major surgical complications (anastomotic leak) in the group of patients that demonstrated histopathological regression grades 3 and 2. In contrast to this finding, Maggiori et al. describe a lower anastomotic leakage rate among patients with pathological complete response (pCR). In the populations described by Landi et al and Duldulao et al no associations were found between pathological response and postoperative complications[7,8].

When considering a more conservative treatment strategy for a patient with clinical complete response it is important to know whether response to nCRT is related to an increased or decreased postoperative complication rate. Pre-operative risk assessment based on individual patient characteristics allows for a more accurate consideration of potential harm and benefit of the different treatment strategies.

Because of discordant results on the postoperative morbidity associated with response to nCRT and its potential influence on clinical decision making, we aimed to clarify whether there is a causal relation between response to nCRT and surgical complications. In order to investigate this, surgical complication rates were compared between patients with and without pCR in a nationwide and unselected cohort of patients that underwent TME after nCRT. Because the nature of surgical complications differs markedly between patients with or without the construction of a primary anastomosis (risk of anastomotic leak), these groups were analysed separately.

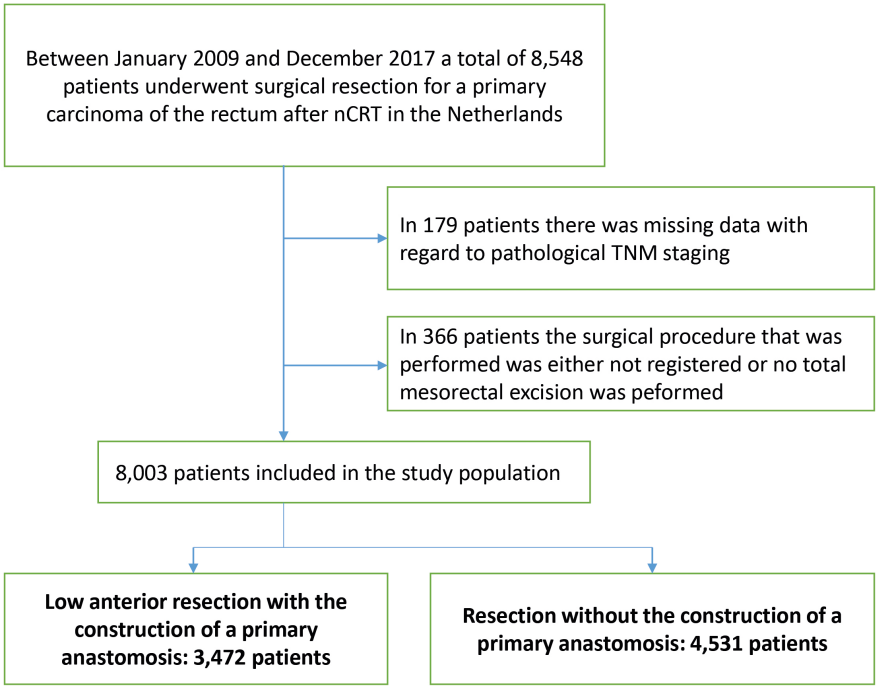
MATERIALS AND METHODS

Patients

Data were obtained from the Dutch ColoRectal Audit (DCRA, www.dica.nl/dcra) database. The DCRA was initiated by the Association of Surgeons of the Netherlands in order to monitor, evaluate and improve colorectal cancer care. Because participation in the DCRA is made mandatory by the Dutch Health Care Inspectorate, all 92 hospitals performing colorectal cancer surgery in the Netherlands participate in data delivery to this nation-wide database. As a consequence, in this database, data are recorded on all patients that undergo colorectal cancer surgery in the Netherlands. Data are recorded on over 200 parameters including; demographic characteristics, pre-operative work-up, pre-operative clinical staging, procedures performed, postoperative complications encountered and results of pathological examination. Validity of the data is safeguarded by control tools in the web-based data entry program. Feedback is sent whenever data was missing or appeared to be improbable. Furthermore, an annual comparison is made with the National Cancer Registry on completeness and accuracy[9]. Patients were selected from the database when they met the following criteria; (1) having undergone surgical resection of a single primary carcinoma of the rectum during the period from January 1 2009 to December 31 2017, (2) having undergone nCRT before surgery. Minimal data requirements for inclusion in the study were data completeness on; postoperative tumour staging, detailed information on the exact procedure that was performed and whether or not a primary anastomosis was constructed. Patients were divided into two groups; patients that underwent TME without the construction of a

primary anastomosis (APR and LAR without anastomosis) and patients that underwent TME with the construction of a primary anastomosis (Figure 1). As this was an observational study, and study data could not be traced back to individual patients, the study received ethical review board exemption status.

Figure 1 Patient inclusion



Treatment

In the Netherlands, patients with a locally advanced rectum carcinoma are treated with nCRT according to the current national guidelines. According to these guidelines radiation therapy is given at a total dose of 45 to 50 Gy (delivered in daily 1.8-2 Gy fractions 5 days per week). During radiation therapy, chemotherapy is given on a daily base (capecitabine 825-1000 mg/m2 5-7 days per week). Usually, surgical resection according to TME principle is performed 8 to 12 weeks after completion of the radiation therapy. The procedures performed are done in either a laparoscopic or open fashion depending on surgeon preference and tumour characteristics.

Main outcome:

The primary outcome parameter was the occurrence of one or more surgical complication within 30 after surgery or during the concerning hospital admission (including mortality). Surgical complications were defined as complications that were directly related to the procedure that was performed. Complications that were scored were; anastomotic leak, pelvic abscess, surgical site infection, postoperative haemorrhage, ileus requiring surgical intervention, fascial dehiscence and iatrogenic injury of bowel or urinary tract.

Secondary outcome parameters that were investigated were; the occurrence of one or more post-operative complications regardless of cause within 30 days after surgery or during the concerning hospital admission, the occurrence of anastomotic leakage, one or more invasive procedure performed due to post-operative complication (including both surgery and placement of percutaneous drains), anastomotic take down resulting in secondary stoma construction and the occurrence of one or more non-surgical complication within 30 days after surgery or during the concerning hospital admission.

Anastomotic leak was defined requiring either radiological or surgical intervention (ISREC grade B and C). Because no routine imaging was performed, patients with grade A anastomotic leakage were not scored and were therefore automatically analysed as having no anastomotic leakage.

Non-surgical complications were scored and defined as complications of either a; cardiac, respiratory, thromboembolic, infectious (other than surgical site) and neurologic nature. Mortality was defined as mortality of any cause, within 30 days after surgery or during the course of the concerning hospital admission.

Predictors and confounders:

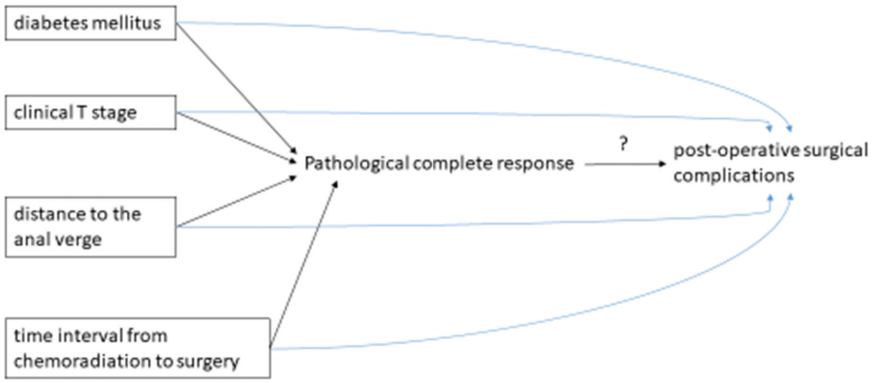
The main predictor that was investigated in this study was pathological response to nCRT. For this, pathological response was categorized into two groups; patients with and patients without pCR. Pathological complete response was defined as the absence of histological evidence of viable tumour cells at the

primary tumour site or loco regional lymph nodes in the resected specimen (ypT0N0). There was no detailed information available on tumour regression grade. Patients with moderate, minimal and poor response were therefore grouped together as no pCR.

Confounders were defined as parameters that are both associated with the exposure; pCR and the primary outcome parameter; surgical complications without being in the causal path. Four parameters were considered to be potential confounders. Figure 2 displays a directed graph in which the relations between the confounders, exposure and outcome are illustrated.

Parameters that were considered to be confounders were; diabetes mellitus10-13 (dichotomous variable), tumour size reflected by clinical T stage14,15 (analysed as a categorical variable; 4 subgroups), distance to anal verge16,17 (analysed as a categorical variable defined as low (0-5cm), mid (>5-10cm) and high (>10cm) tumours) and time interval from nCRT to surgery in weeks18,19 (analysed as a continuous variable).

Figure 2: Graphical presentation of confounding in directed acyclic graph



Arrows are drawn based on prior knowledge of causal relationships between parameters. Boxed parameters are related to both pathological complete response and post-operative surgical complications and are outside the causal chain. Therefore boxed parameters considered to be confounders. The research question is indicated with a question mark above the arrow from exposure (pCR) to outcome (post-operative surgical complications).

Handling of missing data

Three of the confounders that were entered in the multivariable analyses contained missing data; distance to the anal verge (missing in 975 patients, 12.18%), clinical T stage (missing in 310 patients, 3.87%) and time interval from nCRT to surgery (missing in 694 patients, 8.67%). In 6.211 patients (77.61%), data was complete on all of these variables.

Little's missing completely at random (MCAR) test was performed in order to investigate whether missing data could be assumed to be MCAR. As Little's MCAR test was not significant (Chi-Square = 33.623, df = 0, sig.= 0.000), missing data could not be assumed to be MCAR. Since missingness was over 5% and data could not be considered to be MCAR, complete case analysis was considered to be an unacceptable approach[20]. For this reason, multiple imputation by fully conditional specification was performed to impute estimated values for the three variables containing missing data that were considered to be potential confounders.

Statistical analysis

The study population was divided in patients with and without the construction of a primary anastomosis after TME. These groups were described and analysed separately. Within these groups overall and specified complication rates were stratified by pathologic response. The association of pCR with each of the outcomes of interest was analysed using univariable and multivariable logistic regression models. In the multivariable models, all of the parameters that were identified in the directed graph (Figure 2) were included regardless of statistical significance.

This way, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. P-values under 0.05 were considered to be statistically significant. All calculations were performed using the Statistical Package for the Social Sciences (SPSS) version 23 (Chicago, IL, USA).

RESULTS

From January 1 2009 until December 31 2017, a total of 8,548 patients were identified in the DCRA database that underwent colorectal resection for colorectal cancer. Minimal data requirements were met for 8,003 patients. All of these patients underwent nCRT before resection of the tumour through either TME with anastomosis (3,472 patients, 43.4%) or TME without anastomosis (4,531 patients, 56.6%). Figure 1 displays a detailed representation of the inclusion process.

Overall, pCR was observed in 976 (12.2%) patients. Furthermore, the majority of patients (in both groups) were male (5,102 patients, 63.8%), aged between 60 and 70 (2,959 patients, 37.0%), ASA class 2 (4,897 patients, 61.2%) and underwent resection for a clinically (pre-treatment) staged T3/T4 adenocarcinoma (7,076 patients, 88.4%) (not in table). In the overall population of patients in-hospital mortality was 1.2% (94 patients) and did not differ between patients with and without pCR (p=0.171). Overall, more complications (surgical and non-surgical together) were observed in the group with pCR (319 patients, 32.7% versus 2,103 patients, 29.9%). This difference was not statistically significant (p-value 0.083, not in table). Surgical complications were more frequently observed when pCR was present (242 patients, 24.8% versus 1,396, 19.9%, p-value <0.001).

The patient characteristics of the TME with anastomosis and TME without anastomosis group are summarized in Table 1.

Table 1 Patient and disease characteristics (N(%), unless specified otherwise)

	TME with anastomosis N=3,472	TME without anastomosis N=4,531
Male sex	2,192 (63.1%)	2,910 (64.2%)
Age (years; mean (SD))	62.4 (10.1)	65.7 (10.3)
Type of procedure		
LAR with anastomosis	3,472 (100%)	
LAR without anastomosis	-	1,235 (27.3%)
APR	-	3,296 (72.7%)
Laparoscopic (assisted) procedure	2,288 (65.9%)	2,441 (53.9%)
Creation of defunctioning stoma	2,601 (74.9%)	-
ASA classification		
1	1,016 (29.3%)	1,002 (22.1%)
2	2,134 (61.5%)	2,763 (61.0%)
3	302 (8.7%)	717 (15.8%)
4	8 (0.2%)	26 (0.6%)
Missing data	12 (0.3%)	23 (0.5%)
Medical history		
Diabetes Mellitus	383 (11%)	651 (14.4%)
Cardiac	404 (12.7%)	806 (17.8%)
Pulmonary	323 (9.3%)	499 (11%)
Pre-operative anaemia*	357 (10.3%)	567 (12.5%)
BMI		
<20	171 (4.9%)	253 (5.6%)
20-24	1,334 (38.4%)	1,584 (35.0%)
25-34	1,754 (50.5%)	2,286 (50.5%)
≥35	94 (2.7%)	168 (3.7%)
Missing data	119 (3.4%)	240 (5.3%)
Distance to the anal verge (cm)		
0-5	616 (17.7%)	2,820 (62.2%)
>5	2,446 (70.4%)	1,146 (25.3%)
Missing data	410 (11.8%)	565 (12.5%)
Pathological T stage		
T0	629 (18.1%)	768 (17%)
T1	217 (6.3%)	289 (6.4%)
T2	833 (24.0%)	1,169 (25.8%)
T3	1,654 (47.6%)	1,968 (43.4%)
T4	139 (4.0%)	337 (7.4%)

Table 1 Continued

	TME with anastomosis N=3,472	TME without anastomosis N=4,531
Median time interval nCRT to surgery (weeks)	15	15
Pathological N stage		
N0	2,265 (65.3%)	3,081 (68.0%)
N1	795 (22.9%)	967 (21.3%)
N2	412 (11.9%)	483 (10.7%)
Pathological M stage		
M0	3,266 (94.1%)	4,149 (91.6%)
M1	206 (5.9%)	382 (8.4%)
Pathologic complete response	443 (12.8%)	533 (11.8%)
Histologic subtype		
Adenocarcinoma	3,229 (93.0%)	4,062 (89.6%)
Mucinous carcinoma	124 (3.6%)	233 (5.1%)
Other/ non-specified	119 (3.4%)	236 (5.2%)

LAR: low anterior resection; APR: abdominoperineal resection; ASA: American Society of Anesthesiologists; BMI: body mass index

* defined as preoperative haemoglobin levels<11.3 g/dL in male patients and haemoglobin levels<10.5 g/dL in female patients

Apart from the mean distance to the anal verge and surgical procedure performed, the baseline parameters appear to be comparable between both groups. Mean distance to the anal verge was shorter in the TME without anastomosis group (4.3 cm vs. 8.4 cm).

Results TME with primary anastomosis group

A total of 3,472 patients underwent anterior resection with the creation of a primary anastomosis after nCRT during the study period. In the large majority of these patients, also a defunctioning stoma was created (74.9%). The first two columns of Table 2 demonstrate how postoperative outcome parameters differed between patients with and without pCR.

Table 2 Postoperative outcomes stratified for pathological response

	After TME with primary anastomosis (N=3,472)		After TME without primary anastomosis (N=4,531)	
	No pCR n=3,029	pCR n=443	No pCR n=3,998	pCR n=533
Surgical complications	598 (19.7%)	122 (27.5%)	798 (20.0%)	120 (22.5%)
In-hospital mortality	26 (0.9%)	2 (0.5%)	63 (1.6%)	3 (0.6%)
All complications	873 (28.8%)	159 (35.9%)	1,230 (30.8%)	160 (30.0%)
Anastomotic leak ISREC grade B/C	173 (5.7%)	35 (7.9%)	-	-
Invasive procedure due to complication	353 (11.7%)	60 (13.5%)	361 (9.0%)	57 (10.7%)
Anastomotic take-down	125 (4.1%)	23 (5.2%)	-	-
Non-surgical complications	500 (16.5%)	71 (16.0%)	717 (17.9%)	76 (14.3%)
Median length of stay in days (range)	7 (2 – 191)	7 (2 – 65)	8 (2 – 185)	7 (2 – 80)

Data are numbers and percentages in parentheses unless indicated otherwise

pCR: pathologic complete response; ISREC: International Study Group of Rectal Cancer

Overall postoperative complications were more often observed in patients that demonstrated pCR (difference of 7.1%). Overall, more surgical complications were observed in the pCR group (122 patients (27.5%) with pCR developed a postoperative surgical complication compared to 598 patients (19.7%) in the no pCR group). This difference was found to be statistically significant in univariable analysis (p-value 0.003). A more detailed exploration of the specific surgical complication rates revealed that anastomotic leak was more frequently observed when pCR was present (5.7% versus 7.9% in the pCR group). Furthermore, surgical re-intervention and secondary stoma construction were more frequently observed in the pCR group. The results of univariable logistic regression analyses are demonstrated in Table 3.

Surgical complications were observed more often when pCR was present (OR $_{\text{univariable}}$ 1.55, 95% CI 1.23-1.94). No statistically significant differences were observed regarding non-surgical complications. The results of the multivariable analyses are demonstrated in Table 4.

Table 3 Univariable analyses of the association between pCR and postoperative outcomes

	After TME with primary anastomosis (N=3,472)			After TME without primary anastomosis (N=4,531)		
	Odds ratio*	95% CI	p-value	Odds ratio*	95% CI	p-value
Surgical complications	1.55	1.23 – 1.94	0.000	1.17	0.94 – 1.45	0.169
Mortality	0.52	0.12 – 2.2	0.379	0.35	0.11 – 1.13	0.080
All complications	1.38	1.12 – 1.71	0.002	0.97	0.79 – 1.17	0.726
Anastomotic leak ISREC grade B/C	1.51	1.05 – 2.17	0.037	-	-	-
Invasive procedure due to complication	1.19	0.89 – 1.59	0.252	1.21	0.90 – 1.62	0.213
Anastomotic take-down	1.27	0.81 – 2.01	0.301	-	-	-
Non-surgical complications	0.97	0.74 – 1.27	0.799	0.76	0.59 – 0.98	0.036

pCR: pathological complete response; ISREC: International Study Group of Rectal Cancer
*Odds ratio estimated based on results of univariable logistic regression analyses with no pCR as the reference group

Table 4 Results of multivariable analyses of the association between pCR and outcome parameters after TME with the construction of a primary anastomosis

Outcome	OR*	95% CI	p-value
Surgical complications	1.53	1.22 – 1.92	0.000
All complications	1.38	1.12 – 1.70	0.003
Anastomotic leak	1.41	1.03 – 2.05	0.040
Invasive procedure due to complication	1.17	0.87 – 1.57	0.296
Anastomotic take-down	1.24	0.78 – 1.96	0.359
Non-surgical complications	0.97	0.74 – 1.28	0.838

pCR: pathologic complete response; TME: Total Mesorectal Excision; OR: odds ratio; CI: confidence interval;
* ORs estimated with no pCR as the reference group for each outcome. Parameters entered in multivariable logistic regression analyses: pCR, distance to anal verge, time interval from chemoradiation to surgery, clinical T stage and diabetes mellitus.

The table demonstrates the ORs of pCR (with no pCR as a reference; OR=1) for each of the outcomes of interest adjusted for the pre-defined potential confounders. Pathological complete response was found to be a statistically significant predictor for the occurrence of surgical complications (lower bound CI OR>1). This was also the case for the outcome parameter anastomotic leakage. There was no significant relation with non-surgical complications.

Results TME without primary anastomosis group

A total of 4,531 patients underwent a resection without anastomosis. The third and fourth column of Table 2 demonstrate how complication rates differed between the response groups. Overall, similar complication rates were observed in both groups. With regard to surgical complications; more were observed in the pCR group (22.5% vs. 20%). Interventions were also slightly more often observed in the pCR group (10.7% vs. 9.0%). In contrast to this finding (and to the results in the primary anastomosis group); more non-surgical complications were observed in the no pCR group (17.9% vs 14.3%). In the no pCR group the percentage of patients that were classed ASA III/IV was also higher compared to the percentage of ASA III/IV patients in the pCR group (17.0% vs. 13.0%). Table 3 demonstrate the results of univariable analyses. For overall surgical complication rates the 95% CI of the OR included 1, indicating no statistically significant effect of pCR on the occurrence of surgical complications. For non-surgical complications a statistically significant OR in favour of no pCR was found. The effect of pCR on surgical complications remained statistically not significant in multivariable analyses (Table 5).

Table 5 Results of multivariable analyses of the association between pCR and outcome parameters after TME without the construction of a primary anastomosis

Outcome	OR*	95% CI	p-value
Surgical complications	1.17	0.94 – 1.46	0.154
All complications	0.98	0.80 – 1.19	0.806
Invasive procedure due to complication	1.22	0.91 – 1.65	0.183
Non-surgical complications	0.80	0.62 – 1.04	0.096

pCR: pathologic complete response; TME: Total Mesorectal Excision; OR: odds ratio; CI: confidence interval; * ORs estimated with no pCR as the reference group for each outcome. Parameters entered in multivariate logistic regression analyses: pCR, distance to anal verge, time interval from chemoradiation to surgery, clinical T stage and diabetes mellitus.

Again, there was only a statistically significant relation between pCR and non-surgical complications.

DISCUSSION

Patients who underwent TME and anastomosis had a higher probability of having postoperative surgical complications when pCR was present. In-depth

analysis demonstrated that this increase in surgical complications was partly caused by an increased risk of anastomotic leakage. Possibly as a result, surgical re-interventions and anastomotic take down were more frequently observed when pCR was present in this patient group. There was no evident relation between surgical complications and pCR when no primary anastomosis was created.

To our knowledge, four studies have been published on postoperative morbidity in relation to response to nCRT [5-8]. The studies done by Landi at al. and Duldulao et al. found no differences in terms of major postoperative complications between patients with and without pCR. As mentioned before, in the population that was described by Maggiori et al. significantly more Clavien Dindo grade III/IV complications were observed in the no-pCR group. In the study done by Horisberger et al. an increased risk on anastomotic leakage among the patients with histologic regression grade 2 and 3 (tumour regression grading as defined by the Japanese Society for Cancer of the Colon and Rectum[21]) was observed [6]. The database did not contain information on histopathologic response grade but the presence of pCR was recorded.

Increasing the interval between nCRT and TME to a minimum of 8 weeks appears to increase pCR and down-staging rates, and improved disease-free survival[22]. Whether an increased interval leads to more tissue reaction and consequently complications, is unclear. Data from the GRECCAR 6 study suggest that more complications are encountered when the interval between nCRT and surgery is longer[23]. In contrast to this finding, the Stockholm III trial found in their pooled analysis of the two short-course radiotherapy regimens (5 × 5 Gy radiation dose with surgery within 1 week versus 5 × 5 Gy radiation dose with surgery after 4-8 weeks) that the risk of postoperative complications was significantly lower after short-course radiotherapy with delay[24].

The nCRT protocols that are currently being described in the literature demonstrate significant tumour downsizing in up to two-third of patients and pathologic complete response (pCR) rates ranging between 14 and 25% [25-27].

The overall pCR rate that was observed in our study is somewhat lower (12.2%). The higher pCR rates described in the literature are all documented in sub populations instead of a nationwide sample. A meta-analysis in which patients with pCR were compared to non-responders found that it was associated with fewer local recurrences, less frequent distant failure and a greater likelihood of being alive and disease-free at 5 years [28]. In addition, due to improved tumour downstaging, relatively more sphincter preserving procedures may be performed after nCRT [29]. In contrast, to this improved oncological outcome nCRT followed by TME surgery has been associated with increased postoperative surgical morbidity [30] and decreased long-term functional outcome[31]. Furthermore, anastomotic leak has been associated with an increased risk on local recurrence, decreased long term survival and decreased disease free survival [32-35].

An alternative treatment strategy is organ preservation through local excision after a good response to nCRT[36,37]. In the GRECCAR 2 study patients that responded well to nCRT (estimated residual tumour < 2cm) were randomised between TME resection and local resection only. In the local excision group a relatively large percentage of patients underwent a completion TME resection. Probably because of this surgical morbidity was increased and compromised the potential advantages of local excision. No short-term superiority of local excision over TME could be established and long term oncological outcome remains to be determined [38]. A similar observation was made by Debove et al. In their study on the results of local excision they also observed relatively high incomplete oncologic treatment results [39]. These findings underline the importance of accurate post nCRT staging when making decisions with regard to subsequent resection strategies.

The present study has several limitations. Although the database was based on a large nationwide population resulting in high statistical significance, the presented results should be interpreted with caution. Response to nCRT was evaluated based on the results of pathological examination of the resected specimen. Unfortunately, it is still difficult to estimate whether pCR is present after nCRT based on clinical parameters. Several studies have investigated

the role of imaging modalities such as transrectal endoscopic ultrasound, magnetic resonance imaging, and integrated positron emission tomography. None of these modalities have proven to accurately diagnose pCR[40-43]. The time sequence of events makes it impossible to use pCR clinically when deciding about whether or not to operate on a certain patient.

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CHAPTER 4

Predicting postoperative mortality after colorectal surgery: a novel clinical prediction model

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ABSTRACT

Aims: The aim of this study was to develop and externally validate a clinical, practical and discriminative prediction model designed to estimate in-hospital mortality for patients undergoing colorectal surgery.

Methods: All consecutive patients that underwent elective or emergency colorectal surgery from 1990 to 2005, at the Zaandam Medical Centre, the Netherlands, were included in this study. Multivariate logistic regression analysis was performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs) linking the explanatory variables to the outcome variable in-hospital mortality, and a simplified Identification of Risk in Colorectal Surgery (IRCS) score was constructed. The model was validated in a population of patients that underwent colorectal surgery from 2005 to 2011, in Barcelona, Spain. Predictive performance was estimated by calculating the area under the receiver operating characteristic (AUC ROC) curve.

Results: The strongest predictors of in-hospital mortality were; emergency surgery (OR=6.7, 95%-CI: 4.7-9.5), tumor stage (OR=3.2, 95%-CI: 2.8-4.6), age (OR=13.1, 95%-CI: 6.6-26.0) pulmonary failure (OR=4.9, 95%-CI: 3.3 – 7.1) and cardiac failure (OR=3.7, 95%-CI: 2.6-5.3). These parameters were included in the prediction model and simplified scoring system. The IRCS model predicted in-hospital mortality and demonstrated a predictive performance of 0.83 (95% C.I.; 0.79 – 0.87) in the validation population. In this population the predictive performance of the CR-POSSUM score was 0.76 (95% C.I.; 0.71 – 0.81)

Conclusions: The results of this study have shown that the IRCS score is a good predictor of in-hospital mortality after colorectal surgery despite of the relatively low number of model parameters.

INTRODUCTION

Systematic analysis of outcome data is essential to evaluate and improve the quality of perioperative care in patients undergoing colorectal surgery[1,2]. Operative mortality is an objective measure that is often used to evaluate the outcome of surgery[3]. However, by comparing crude mortality rates, differences in disease severity are not taken into account. In order to make a valid comparison between centers it is therefore crucial to correct for case-mix[4]. In the past years comparative audit has become an essential part of colorectal surgery. This is reflected in the wide variety of specialty specific scoring systems developed in the past decades [3,5-11]. Furthermore, risk scoring systems may be used to identify patients that are at increased risk for developing complications [12-14]. These patients may benefit from early identification and additional perioperative monitoring or treatment [15-19]. Using an inadequate or outdated prediction model can have serious consequences; for example patients and clinicians can make suboptimal decisions or hospitals can be mistakenly identified as poor performers. The loss of model calibration over time necessitates some form of model update.

The most widely used surgery scoring system is probably the Portsmouth-Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (P-POSSUM)[20,21]. This system uses a 12-factor, 4-grade physiologic score and a 6-factor, 4-grade operative severity score. Several modified versions of the POSSUM scoring system have been designed to meet the requirements of certain surgical subspecialties[3,22-24]. For a scoring system to be useful in current clinical practice it needs to be practical, simple in use and discriminative. Furthermore it must rely on objective data that are readily available.

The aim of this study was to fit a clinical prediction model for postoperative mortality after colorectal surgery that is practical, simple in use and discriminative. Most current models have strong and weak points and share an overlap in model parameters (for example all models contain a parameter based on patient age or mode of surgery). We chose to fit a completely new

model based on candidate predictor variables used in previous studies and additional parameters.

Furthermore, we wanted to externally validate and compare the model to the CR-POSSUM score which is a well accepted but more elaborate risk scoring instrument.

MATERIALS AND METHODS

First, a clinical prediction model was created in a Dutch population of patients that underwent colorectal surgery. Based on this model a simplified scoring system was created; the Identification of Risk after Colorectal Surgery score (IRCS). Both the prediction model and scoring system were externally validated in a population of patients that underwent colorectal surgery in Barcelona, Spain.

Model development population

All consecutive patients that underwent elective or emergency colorectal surgery from 1990 to 2005, at the Zaandam Medical Centre (ZMC), The Netherlands, were included in this study. The ZMC is a teaching hospital serving a population of approximately 185.000 persons in a well defined area. During the study period a 24hr emergency room, a level two intensive care unit and operating theatre facilities were available. Data was collected prospectively in a digital database. The database was kept in parallel with the hospital registration database, recorded in the National Medical Registration (Landelijke Medische Registratie).

Model validation population

Generalizability of the scoring system was assessed by applying it to a different data set consisting of patients that underwent colorectal surgery at Hospital Universitari Vall d'Hebron in Spain. This teaching hospital serves a population of approximately 500,000 persons in the Barcelona area. All consecutive patients were included that underwent colorectal surgery between June 1, 2005, and

July 31, 2011. In this validation group we investigated the predictive performance of both the IRCS score and CR-POSSUM score.

Collected data

Data were recorded considering; age, gender, type of surgical procedure, acute admission, emergency surgery (surgery required and undertaken within 24h after acute admission), underlying disease (benign or colorectal cancer stage), pre-operative systolic blood pressure, preoperative pulse rate, Glasgow Coma Scale. Furthermore, data were collected with regard to; signs and symptoms of cardiac failure (mild: diuretic, digoxin, antianginal or antihypertensive therapy; intermediate: peripheral edema and/ or warfarin therapy; severe: elevated venous jugular pressure and/or the presence of cardiomegaly on chest X-ray) and respiratory status (no dyspnea, dyspnea on exertion or at rest and/or mild evidence of COPD on chest X-ray, limiting dyspnea after walking one flight of stairs, dyspnea at rest) upon admission by the attending ward physician. During surgery, peritoneal soiling (none, local or free purulent soiling) and total blood loss (≤100 ml, 101-500 ml, 501-999 ml or ≥1000 ml) were documented and scored by the operating surgeon. The Primary outcome variable was in-hospital mortality which was defined as mortality of any cause, in the course of the concerning hospital admission.

Statistical analysis

Construction of the scoring system

The influence of time on mortality was investigated by dividing the inclusion period in three equal intervals (1990 to 1994, 1995 to 1999 and 2000 to 2005) and comparing mean mortality within these groups using a one way analysis of variance. Univariate analysis was performed to identify predictors for the primary outcome variable; in-hospital mortality. Continuous variables were categorized into subgroups representing strata of increased risk. Subgroups were compared using the unadjusted odds ratio (OR). The group representing the lowest risk on mortality was considered to be the reference group (OR=1). After univariate analysis a multiple logistic regression analysis was performed linking the explanatory variables to the primary outcome variable. Parameters with a P-value under 0.250 in univariate analysis were entered in the model

using a backward stepwise approach. A backward stepwise approach was favored over a forward stepwise approach in order to reduce the risk of making a type I error in parameter selection. Parameters that were included in the final model were selected based on the Akaike information criterion. Based on the regression coefficients of this model a simplified scoring system was created; the Identification of Risk after Colorectal Surgery (IRCS) score.

Validation of the scoring system

Both the regression model and scoring system were evaluated in the external validation population. IRCS and CR-POSSUM predicted mortality were calculated for all patients in this population. Discriminative performance was assessed by calculating the area under the receiver operating characteristic (AUC ROC) curve (C-statistic)[25]. An AUC ROC of 0.5 represents no discriminative capacity whilst an AUC of 1.0 represents the perfect test (sensitivity and specificity of 100%). Values above 0.8 are considered to represent good discriminating capacity[25]. Calibration of the model refers to the ability of the model to accurately predict the outcome variable in patient subgroups. Model calibration of the CR-POSSUM and IRCS score was evaluated with a calibration plot. This plot shows the relation between observed and predicted mortality.

As this was an observational study, and patient data were stored in a hospital database from which data could not be reduced to individual patients, the study received ethical review board exemption status for both the development and validation population[26].

P-values under 0.05 were considered to be statistically significant. All calculations were performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 (Chicago, IL, USA).

RESULTS

Between January 1990 and August 2005 a total of 1604 patients underwent colorectal surgery at the ZMC. All patients were included in the study. Table 1 demonstrates the patient characteristics of this group.

Table 1 Patient and disease characteristics of development and validation data sets

	Development data set N=1604	Validation data set N=1252
Sex (male)	758 (47.3)	704 (56,1)
Age (years)		
≤ 60	463 (28.9)	329 (26.3)
61-70	353 (22.0)	325 (26.0)
71-81	490 (30.5)	424 (33.9)
>81	298 (18.6)	174 (13.9)
Emergency surgery:		
No	1238 (77.2)	1081 (86,3)
Yes	366 (22.8)	171 (13.7)
Cardiac failure		
None or mild	989 (61.7)	1189 (95.0)
Moderate/ severe	615 (38.3)	63 (5.0)
Pulmonary failure		
None or mild	1506 (93.9)	1162 (92.8)
Moderate/ severe	98 (6.1)	90 (7.2)
Systolic blood pressure (mmHg)		
100-170	1512 (94.3)	**
> 170 or 90-99	78 (4.9)	
< 90	14 (0.9)	
Pulse per minute		
40-100	1531 (95.4)	**
101-120	62 (3.9)	
> 120 or < 40	11 (0.7)	
Peritoneal soiling		
None or serous fluid	1454 (90.6)	**
Local pus/ free pus or feces	150 (9.4)	
Procedure		
Colectomy	436 (27.2)	515 (41.1)
Sigmoid resection	541 (33.7)	252 (20.1)
Anterior resection	167 (10.4)	293 (23.4)
Abdominoperineal resection	66 (4.1)	66 (5.3)
Colostomy	125 (7.8)	51 (4.1)
Other	269 (16.8)	75 (6.0)
Underlying disease *		
No malignancy or colorectal malignancy stage I/II	1030 (64.2)	884 (70.6)
colorectal malignancy stage III/IV	574 (35.8)	368 (29.4)
median length of stay (days)	14	8

Values in parentheses are percentages unless indicated otherwise

* tumor staging according to AJCC/UICC

** the database that was used for validation did not provide any information on these variables

Postoperative mortality was 9.1 % (146 patients). Of these, 64(43.8%) underwent one or more reoperations because of a surgical complications. In 35% of cases mortality was directly related to a cardiac complication. Median time to death was 11 days Postoperative mortality was 24.3 % in patients that underwent emergency surgery and 4.6 per cent in patients that underwent elective surgery. From 1990 to 1994, 1995 to 1999 and 2000 to 2005 mortality rates were respectively; 9%, 9% and 8%, Mortality rates did not differ significantly between groups (p-value 0.82).

The unadjusted odds ratios of the candidate predictor variables for mortality are demonstrated in Table 2.

Table 2 Patient and disease characteristics predicting in-hospital mortality; results of univariate and multivariate logistic regression

Candidate predictor variable	Univariate analysis overall p-value OR (95% CI)	Multivariate analysis overall p-value OR (95% CI)
	<0.001	<0.001
Age (years)		
≤ 60	1	1
61-70	2.4 (1.1 – 5.3)	1.6 (0.7 – 3.7)
71-81	5.3 (2.6 – 10.5)	3.2 (1.5 – 6.7)
> 81	13.1 (6.6 - 26.0)	6.6 (3.1 – 13.9)
	<0.001	<0.001
Emergency surgery		
No	1	1
Yes	6.7 (4.7 - 9.5)	6.2 (4.0 – 9.6)
	<0.001	<0.001
Underlying disease *		
No malignancy or colorectal malignancy stage I/II	1	1
colorectal malignancy stage III/IV	3.2 (2.8 – 4.6)	4.2 (2.7 – 6.4)
	<0.001	<0.001
Cardiac failure		
None or mild	1	1
Moderate/ severe	3.7 (2.6 – 5.3)	2.5 (1.7 – 3.9)
	<0.001	<0.001
Pulmonary failure		
None or mild	1	1
Moderate/ severe	4.9 (3.3 – 7.1)	3.3 (2.1 – 5.2)

Table 2 Continued

Candidate predictor variable	Univariate analysis overall p-value OR (95% CI)	Multivariate analysis overall p-value OR (95% CI)
	<0.001	**
Systolic blood pressure (mmHg)		
100-170	1	
> 170 or 90-99	2.5 (1.3 – 4.5)	
< 90	20.3 (6.7 – 61.6)	
	<0.001	**
Pulse per minute		
40-100	1	
101-120	3.0 (1.6 – 5.6)	
> 120 or < 40	19.5 (5.6 – 67.6)	
	<0.001	0.01
Peritoneal soiling		
None or serous fluid	1	1
Local pus/ free pus or feces	4.0 (2.7 – 6.1)	2.0 (1.2 – 3.6)

Values in parentheses are percentages unless indicated otherwise. OR: odds ratio; CI: confidence interval

* tumor staging according to AJCC/UICC

** variables not significant in multivariate analysis

This table also displays the results of the multivariate analysis. The strongest predictors of mortality included; acute operation, tumor stage, age, pre-operative pulmonary failure and pre-operative cardiac failure. These parameters were included in final model that was thus created:

Odds in-hospital mortality = EXP (- 5.526 + (2.027 × emergency surgery) + (1.317 × underlying disease category) + (0.903 ×cardiac failure) + (1.207y × pulmonary failure) + (0.484 × age 61-70) + (1.181 × age 71-80) + (1.934 × age >80))

The simplified scoring system that was based on this regression model is demonstrated in Table 3.

Table 3 the Identification of Risk in Colorectal Surgery score chart

Variable	Points
Age (years)	
≤ 60	0
61 - 70	1
71 – 80	2
≥ 81	3
Disease category	
No malignancy or stage I/II colorectal cancer	0
Stage III/ IV colorectal cancer	1
Emergency surgery [a]	
No	0
Yes	2
Signs/ symptoms of cardiac failure	
None or mild [b]	0
Intermediate or severe	1
Signs/ symptoms of pulmonary failure	
None or mild	0
Intermediate or severe	1

a Surgery required and taken place within 24 h after admission

b diuretic, digoxin, antianginal or antihypertensive therapy

c intermediate: peripheral oedema and/or warfarin therapy; severe: elevated venous jugular pressure and/or cardiomegaly on chest X-ray

For each parameter points can be scored to calculate the IRCS score.

External validation of the IRCS model and scoring system

Between June 1, 2005, and July 31, 2011, 1252 consecutive patients underwent colorectal surgery at Hospital Universitari Vall d'Hebron in Barcelona (see Table 1, third column). The mean age was 67 years at the time of operation. The majority of patients underwent elective colorectal surgery (1081, 86.3 %). A total of 77 patients died after surgery. In 21 cases (27%) mortality was directly related to a cardiopulmonary complication. Postoperative mortality was 18.1 per cent in patients that underwent emergency surgery and 4.2 per cent in patients that underwent elective surgery.

Table 4 demonstrates the discriminative performance of the CR-POSSUM and IRCS scoring systems expressed as the AUC ROC curve for mortality.

Table 4 Discriminative performance of the CR-POSSUM and IRCS score

Scoring system	AUC ROC	95% CI
IRCS score	0.83	0.79 – 0.87
CR-POSSUM score	0.76	0.71 – 0.81
ASA-classification	0.69	0.63 – 0.75

AUC: area under the receiver operating characteristic; CR-POSSUM: ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity; IRCS: Identification of Risk after Colorectal Surgery

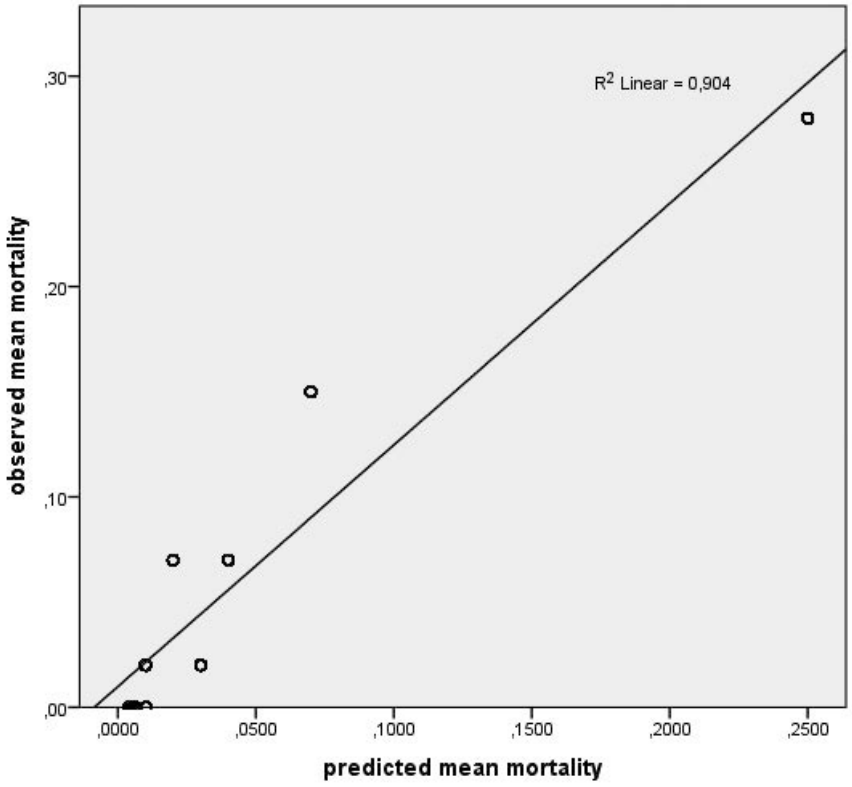
The IRCS model predicted mortality demonstrated a discriminating capacity of 0.83 (95% C.I.; 0.79 – 0.87). In this population the predictive performance of the CR-POSSUM score was 0.76 (95% C.I.; 0.71 – 0.81).

Calibration: The Hosmer and Lemeshow chi-square test was not significant for the IRCS score (7.27, p=0.51) indicating that there was no significant difference between the numbers of observed and expected cases. Calibration of the IRCS model in the external population is graphically demonstrated in the calibration plot (Figure 1).

DISCUSSION

The purpose of this study was to create a practical, simple in use and discriminative scoring system specific to patients undergoing colorectal surgery. For the validation of the model we chose a population of comparable patients with regard to procedures performed and underlying disease category. In order to get a good measure of generalizability, we chose our validation population from a different geographic location in a different time period. The present study shows that the IRCS score is able to stratify patients undergoing colorectal surgery into outcome related groups regarding postoperative mortality. Compared to the CR-POSSUM prediction model, the IRCS score demonstrates improved discriminative performance despite of the lower number of model parameters.

Figure 1 IRCS model calibration plot



Predicted mortalities are demonstrated on the x axis and the actual observed outcome on the y axis. The observed outcome is plotted by deciles of prediction. This makes figure one a graphical illustration of the Hosmer and Lemeshaw test for goodness of fit. Perfect predictions are on a 45 degree angled line.

This is reflected by the AUC of the ROC curve for IRCS predicted in-hospital mortality of 0.83 (95% C.I.; 0.79 – 0.87). Although both populations were comparable with regard to procedures performed and underlying disease category, there were marked differences between the populations. As can be concluded from Table 1, the percentage of patients that were operated on age above 81, was considerable higher in the development population. Furthermore, emergency surgery and cardiac failure were more frequent in the development population. This is reflected by the considerable longer postoperative hospital stay in the development cohort. Even in a different setting, the IRCS remained a valid tool for risk stratification.

The POSSUM and P-POSSUM scoring system have been demonstrated to accurately predict mortality in patients undergoing colorectal surgery[27,28], however lack of calibration has been demonstrated in patients undergoing rectal resection[29], at the extremes of age[30] and after surgery for complicated diverticulitis[31]. Because of this, Tekkis et al. developed a dedicated colorectal POSSUM[3]. The CR-POSSUM score was based on a regression analysis of the original P-POSSUM parameters. To calculate the CR-POSSUM points are scored for six physiological parameters and four operative parameters. The CR-POSSUM score has been evaluated externally extensively with varying results. In some populations it appeared to over-predict mortality[32,33] whilst an under-prediction of mortality was demonstrated in other populations[34]. In addition to the CR-POSSUM score there are several risk prediction models available for patients undergoing colorectal surgery (Table 5).

Table 5 Review of available scoring systems for colorectal surgery

Scoring system	Year*	Outcome	Population	Number of model parameters	Validation	AUC ROC
ACPGBI CRC model[7]	2003	30-day mortality	Colorectal cancer surgery	5	External	0.70[40] 0.73[48]
CR-POSSUM[3]	2004	In-hospital mortality	Patients undergoing colorectal surgery	10	External	0.68[40] 0.78[37] 0.74[49]
CCF-CRC[8]	2004	30-day mortality	Colorectal cancer surgery	6	External	0.81[42]
ACPGBI-MBO model[9]	2004	In-hospital mortality	Surgical treatment for malignant bowel obstruction	4	Internal	0.80
AFC score[43]	2005	In-hospital mortality	colorectal surgery for malignant or diverticular disease	4	External	0.89[11]
Elderly CRC model[10]	2006	30-day mortality	Colorectal cancer surgery	6	Internal	0.73
ACS risk calculator[44]	2009	Overall morbidity/ serious morbidity/ mortality	Patients undergoing colorectal surgery	15	Internal	0.90[44]
Present study	2012	In-hospital mortality	Patients undergoing colorectal surgery	5	Internal External	0.85 0.83

AUC ROC: area under the receiver operating characteristic; CR-POSSUM: Colorectal Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity; ACPGBI CRC: Association of Coloproctology of Great Britain and Ireland Colorectal Cancer; CCF-CRC: Cleveland Clinic Foundation Colorectal Cancer; MBO: Malignant Large Bowel obstruction; AFC: Association Française de Chirurgie; ACS: American College of Surgeons

* Year of publication

One of these is the Association of Coloproctology of Great Britain and Ireland (ACPGBI) Colorectal Cancer Model[7]. It was designed to give an individual risk prediction for 30-day mortality after colorectal cancer surgery. Like the POSSUM models it was created using multiple logistic regression analysis. The model contains five parameters; age, resection status, ASA classification, Dukes classification and operative urgency. External validation of the model demonstrated good predictive performance in patients undergoing elective surgery. However an underestimation of mortality was found in the subgroup of patients undergoing emergency surgery[35,36]. Subsequently the ACPGBI Malignant Large Bowel obstruction model[9] was created using data from 1046 patients undergoing surgery for malignant large bowel obstruction. The model was created specifically to predict in-hospital mortality after surgical treatment of malignant large bowel obstruction. To our knowledge this model did not undergo external validation.

In 2004 Fazio et al. developed the Cleveland Clinic Foundation Colorectal Cancer Model (CCF-CRC)[8]. This model was also based on multiple logistic regression analysis and designed to predict 30-day mortality. Based on the regression model a scoring system was created. Parameters that were included in the risk score were; age, ASA, TNM stage, mode of presentation, hematocrit level and cancer resection. External validation demonstrated good discriminating performance but poor calibration[37]. The Elderly Colorectal cancer model[10] was created to estimate the risk on adverse events in the specific population of elderly patients undergoing colorectal surgery. Life expectancy is increasing and colorectal cancer incidence rises with age. For this reason the question often rises whether to perform major colorectal surgery in this fragile group of patients. Based on a regression model an additive score was created to estimate a patient's risk of postoperative mortality. Parameters are; age, ASA grade, metastases, urgency, tumor resection and large bowel obstruction. The model was validated using split sample technique. In the validation group the model demonstrated good predictive performance in patients older than 80 years undergoing colorectal surgery. However, to our knowledge, the model did not undergo external validation. The Association Française de Chirurgie score[11,38] is a four item predicting score of postoperative

mortality after colorectal resection for cancer or diverticulitis. Model predictors of mortality are; age>70, emergency surgery, loss of body weight more then 10% and neurological comorbidity. Like the IRCS score the AFC score is easy to calculate and contains parameters that are in general readily available. To our knowledge this scoring system has only been validated in France[11].

A more elaborate scoring system is the risk calculator that was developed by the American College of Surgeons (ACS) [39]. Data from the ACS National Surgical Quality Improvement Program (NSQIP) database was analyzed using multiple logistic regression analysis. Fifteen risk factors were identified and included in the model: ASA classification; sepsis; functional health status; preoperative laboratory values of albumin, creatinin and partial thromboplastin time; indication for surgery; disseminated cancer; surgical extent; body mass index; emergency surgery; age; dyspnea; COPD and wound class. The calculator provides an estimate on morbidity, serious morbidity and mortality. Compared to the other prediction models, the ACS risk calculator distinguishes itself by incorporating the influence of hospitals on the outcome. Although the calculator demonstrated a high predictive performance for mortality in the population from which it was created, it requires information on a relatively large number of parameters.

Compared to the CR-POSSUM, ACPGBI CRC, ACS risk calculator and CCF-CRC model, the IRCS model consists of a relatively low number of model parameters. The parameters of the IRCS score are readily available in clinical practice and leave little room for interpretation. Some of the above mentioned scoring systems include the American Society of Anesthesiologists (ASA) preoperative fitness classification of patients[40], the so called ASA score, as a model parameter. The ASA score, is to some extent subjective[41] and therefore induces inter observer variability in the concerning models. Furthermore, some of these models include a tumor staging parameter based on the Dukes classification. The Dukes classification is no longer recommended for clinical practice and has largely been replaced by the TNM system[42] .

The results of this study show that the IRCS score is a good predictor of mortality in patients undergoing colorectal surgery in both the population in which the model was created and in a similar population of patients that were selected from a different geographic location in a different time period. Using hand held computers or phones the regression formula can be used to estimate mortality. In absence of these tools, the scoring system can be used to obtain a rough estimate of mortality.

As can be concluded from Table 1, a large part of patients that were operated on, in both the Netherlands and Spain, were aged over 70 years. Risk prediction models using clinical parameters to calculate scores and probabilities are not the only tools to assess fitness for surgery in this population. Cardiopulmonary exercise testing (CPET) provides a measure of the individual's integrative response to physical stress. Although CPET is a relatively old tool, it provides accuracy to risk assessment and has demonstrated to introduce more effective resource allocation in the perioperative care of elderly patients undergoing major surgery. Furthermore, in this specific population, quality of life and functional outcome are important measures of outcome. Therefore, these measures should be considered when evaluating the quality of care in this group. When making individualized treatment decisions, the expected harm and benefit of surgery should be estimated and evaluated. In order to make a valid comparison between different treatment strategies, the expected effect on quality of life and functional outcome need to be estimated. These potential endpoints were not evaluated in the present study. We therefore recommend that further research on clinical prediction models for patients undergoing colorectal surgery should include quality of life and functional outcome as endpoints.

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CHAPTER 5

Risk factors for postoperative delirium after colorectal operation

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ABSTRACT

Background: A clear understanding of risk factors for postoperative delirium helps in the selection of individuals who might benefit from targeted perioperative intervention. The aim of this study was to identify risk factors for postoperative delirium after colorectal operation for malignancy.

Methods: All consecutive patients who underwent elective or emergency operation because of malignancy of the colon, sigmoid, or rectum between 2009 and 2012 were included in this study. Potential risk factors for postoperative delirium were selected based on previous studies. These candidate factors were analyzed using univariate and multivariate logistic regression analysis. Based on this analysis, odds ratios and 95% confidence intervals were estimated.

Results: A total of 436 patients underwent an oncologic resection of the colon, sigmoid, or rectum. Postoperative delirium was observed in 45 (10.3%) patients. Patients with a delirium had a greater in-hospital mortality rate (8.9% versus 3.6%, P=.09), spent more days in the Intensive Care Unit, and had a longer total hospital stay. Variables associated with postoperative delirium in univariate analyses were: age, American Society of Anesthesiologist classification, blood transfusion, history of psychiatric disease, history of cerebrovascular disease, postoperative pain management, postoperative renal impairment, C-reactive protein levels, leucocyte blood count, and postoperative complications. Independent risk factors were: history of psychiatric disease (odds ratio 8.38, 95% confidence interval; 1.50–46.82), age (odds ratio 4.01, 95% confidence interval; 1.55–10.37) and perioperative blood transfusion (odds ratio 2.37, 95% confidence interval; 1.11–5.06).

Conclusions: This study shows that postoperative delirium is a frequently encountered complication after colorectal operation. Three independent risk factors for postoperative delirium were identified (history of psychiatric disease, age, and perioperative transfusion) that may contribute to risk estimation in this patient population.

INTRODUCTION

Postoperative delirium (POD) is a common and important complication after operation. It is defined as an acutely altered and fluctuating mental status with features of inattention, disturbance, and an altered level of consciousness[1]. The development of delirium during hospital admission is associated with functional decline, longer hospitalization, and institutionalization, and increased mortality[2,3].

Although delirium may occur in patients of any age, it is particularly common among the elderly[1]. In the overall population of hospitalized patients, incidences ranging from 11% to 42% have been reported[4]. Among frail elderly patients, POD has a prevalence of up to 60% after major emergency operation[5]. With the population ageing at an unprecedented rate, the number of operative procedures on the elderly will continue to increase. Additionally, because of improvements in operative and anesthetic care, and the development of less invasive operative techniques, more elderly patients are considered for major colorectal operation. Incidence of POD is therefore expected to increase in the coming decades.

Interventions aimed at reducing the prevalence of delirium in frail elderly patients have proven to be effective[6]. Whether using these preventative measures is effective in reducing POD in the overall population of elderly patients undergoing major operations remains to be determined. A recent study demonstrated no evident effect of structured perioperative measures on POD reduction after major operation for malignancy in the overall population of patients aged > 65[7]. Interventions aimed at reducing risk of POD, however, seem to be more effective when the risk of POD is > 30%[6]. To take full advantage of available resources and employ a cost-effective strategy for POD prevention, interventions should be targeted at high-risk populations. A clear understanding of risk factors might help select individuals at increased risk for POD who might benefit from targeted perioperative intervention.

Risk factors and incidences of POD have been extensively studied in the field of cardiac and orthopedic surgery, yet only a few studies have assessed the incidence and risk factors of POD in the specific population of patients undergoing colorectal operations[8-10]. The aim of this study was to identify independent risk factors for POD in patients after colorectal operation because of a malignancy.

MATERIALS AND METHODS

Population

All consecutive patients aged > 40 who underwent either elective or emergency colorectal resection for malignancy between 2009 and 2012 at University Medical Center Groningen, the Netherlands, were included in this study. University Medical Center Groningen is a tertiary referral center serving a population of approximately one million in the northern part of the Netherlands. As this was an observational study, and patient data were stored in a hospital database from which data could not be reduced to individual patients, the study received ethical review board approval. Patient data were processed and stored according to the Declaration of Helsinki - ethical principles for medical research involving human subjects.

Collected data

During the study period, patient data were collected prospectively and stored anonymously in an electronic database. Stored data consisted of patient demographics, procedure details, and candidate risk factors. Parameters considered as potential risk factors were identified based on study results published previously[8-15].

Candidate risk factors were perioperative blood transfusion (defined as transfusion during the week prior to operation or during postoperative hospital stay), decreased postoperative hemoglobin level, emergency operation (operation required and undertaken within 24 hours of acute admission), duration of anesthesia, postoperative pain management (defined as either epidural analgesia or opioid analgesia, including patient-controlled intravenous

analgesia), Charlson co-morbidity index,[16] American Society of Anesthesiologists (ASA) classification,[17] alcohol abuse (self-reported consumption of >4 units daily average), history of psychiatric disease (mental disorder documented preoperatively by psychiatrist), dementia or early signs of dementia, history of cerebrovascular disease (documented cerebrovascular accident or transient ischemic attack), chronic preoperative use of analgesics, elevated preoperative blood urea nitrogen (>7.5 mmol/L according to local laboratory reference range), postoperative renal impairment defined as glomerular filtration rate (GFR) < 45 ml/min x 1.73m2 (lowest value measured until the third postoperative day), postoperative C-reactive protein (CRP) levels (greatest value measured until the fourth postoperative day, mg/L), postoperative leucocyte count (greatest value measured until the fourth postoperative day, 10^9/l), and postoperative complications (most serious complication during hospital admission according to the Clavien-Dindo classification of surgical complications other than POD). Postoperative CRP levels were dichotomized according to what was assumed to be a normal postoperative response (CRP<150 mg/l) and an elevated postoperative response (CRP≥150 mg/l). The same was done for postoperative leucocyte blood count (normal < 15.0 x 10^9/l, elevated ≥ 15.0 x 10^9/l) and decreased postoperative hemoglobin level (< 2 mmol/l, > 2 mmol/l decrease).

The primary outcome variable was POD, defined as a postoperative disturbance of consciousness with reduced ability to focus, sustain, or shift attention during the concerning hospital admission. Three times a day delirium observation screening (DOS) scores[18] were obtained from all patients. In patients observed to have a DOS score of 3 and greater, the geriatrician was consulted to confirm the POD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria[19].

Patients who developed POD underwent a comprehensive physical examination with additional laboratory testing to identify a possible underlying cause for delirium, such as sepsis, electrolyte imbalance, or pharmacological abnormalities, and were treated when necessary. According to the standardized hospital protocol, haloperidol was the medical treatment of choice for symptom control, supplemented by benzodiazepines when necessary.

Secondary outcome variables were hospital length of stay (HLOS), admittance to the intensive care unit (ICU), duration of stay on the ICU and one-year mortality.

Statistical analysis

Univariate analysis was performed to identify potential risk factors for the primary outcome variable POD. Continuous variables were categorized into subgroups representing strata of increased risk for POD. Subgroups were compared using the unadjusted odds ratio (OR). The group representing the lowest risk for POD was considered to be the reference group (OR = 1). After univariate analysis, a multiple logistic regression analysis was performed linking the explanatory variables to the primary outcome variable. Parameters with a *P* value < .10 in univariate analysis were considered for multivariate analysis.

For 4 parameters, missing data were observed: leucocyte count (13.9%), postoperative GFR (6.8%), postoperative hemoglobin levels (4.3%), and CRP (19.4%). Missing value analysis was conducted by performing Little's missing completely at random test to identify potential patterns in missing data that might bias the analysis. Because the missing completely at random test was not significant (Chi-Square = 62.14, DF = 55, Sig = 0.24), it was concluded that the data were missing at random, and a multiple missing value imputation technique was applied. The robustness of our findings and the validity of the data imputation technique were tested by conducting a sensitivity analysis of our primary results using only patients with complete data.

The Statistical Package for the Social Sciences (SPSS version 20.0; IBM Corp, Armonk, NY) was used for all calculations.

RESULTS

Patient characteristics

Between January 2009 and December 2012, a total of 436 patients underwent an oncologic resection of the colon, sigmoid, or rectum. The patient characteristics are summarized in Table 1.

Table 1 Patient and disease characteristics

Total number of patients	N=436
Sex (male)	246 (56.4)
Age (y)	
40–69	266 (61.0)
70–79	124 (28.4)
> 80	46 (10.6)
Charlson comorbidity index	
0-1	347 (79.6)
2-3	72 (16.5)
4-5	14 (3.3)
6-7	2 (0.5)
8	1 (0.2)
ASA classification	
1	57 (13.1)
2	235 (53.9)
3	136 (31.2)
4	8 (1.8)
Emergency surgery	
No	380 (87.2)
Yes	56 (12.8)
Neoadjuvant therapy	
No	269 (61.7)
Yes	167 (38.3)
Recurrent disease	
No	407 (93.3)
Yes	29 (6.7)
Transfusion	
No	281 (64.4)
Yes	155 (35.6)
Procedure	
Partial colectomy*	191 (43.8)
Total colectomy	12 (2.8)
Anterior resection	73 (16.7)
Abdominoperineal resection	78 (17.9)
Total pelvic exenteration	31 (7.1)
HIPEC	51 (11.7)
Cancer stage†	
I	77 (17.7)
II	119 (27.3)
III	88 (20.2)
IV	152 (34.9)

Values in parentheses are percentages unless indicated otherwise. ASA: American Society of Anesthesiologists; HIPEC: hyperthermic intraperitoneal chemotherapy;

* including right and left hemicolectomy, transversectomy and sigmoid resection;

† tumor staging according to AJCC/UICC.

Median age was 67 years (range 40–90). The majority of patients (N = 380, 87%) were operated on electively for a primary malignancy of the colon or rectum. In most cases, the tumor was an adenocarcinoma (93.5%). Procedures performed ranged from (partial) resection of the colon or rectum to combined resections with hyperthermic intraperitoneal chemotherapy (HIPEC).

Patient outcomes

Overall in-hospital mortality was 4.1% (*n* = 18). The primary outcome variable, POD, was observed in 45 patients (10.3%). In this patient group, in-hospital mortality was 8.9%, greater than the 3.6% observed in the non-POD group (*P* = .09). After 1 year, 82.6% of patients (*n* = 360) were still alive (66% were patients who had POD). During hospital admission 38% (*n* = 165) of patients were admitted to the ICU for ≥ 1 day (range, 1–50, median 1). Median HLOS was 11 days (range, 2-256). Patients with POD spent more days on the ICU (median 0 versus 1 day) and had a longer total HLOS (median 10 versus 19 days).

Identification of risk factors for POD

Table 2 summarizes the unadjusted OR of parameters that were associated with POD.

Table 2 Risk factors for POD; results of univariate analysis

Candidate predictor variable	OR (95% CI)	overall P value
Age (years)		
< 70 (ref)	1	<.001
70–80	1.2 (0.56–2.58)	
> 80	5.38 (2.48–11.69)	
Charlson comorbidity index`		
No comorbidity (0) (ref)	1	.28
Mild/moderate comorbidity (1-2)	1.67 (0.86–3.24)	
Severe comorbidity (≥ 3)	1.55 (0.55–4.36)	
ASA classification		
I/II (ref)	1	.04
III/IV	1.91 (1.02–3.56)	
Emergency surgery		
No (ref)	1	.32
Yes	1.55 (0.68–3.51)	

Table 2 Continued

Candidate predictor variable	OR (95% CI)	overall P value
Transfusion		
No (ref)	1	<.001
Yes	3.81 (2.00–7.27)	
Decreased postoperative hemoglobin levels		
< 2 mmol/l Hb (ref)	1	.56
> 2 mmol/l Hb	1.20 (0.65–2.23)	
Postoperative pain management		
Epidural analgesia (ref)	1	.08
Intravascular opioid analgesia	1.45 (1.10–1.90)	
Alcohol consumption*		
< 5 units (ref)	1	.54
≥ 5 units	2.00 (0.21–19.00)	
History of psychiatric disease		
No (ref)	1	.002
Yes	9.44 (2.28–39.16)	
History of cerebrovascular disease		
No (ref)	1	.005
Yes	3.46 (1.45–8.28)	
Chronic preoperative use of analgesics		
No (ref)	1	.37
Yes	1.79 (0.50–6.44)	
Preoperative blood urea nitrogen		
< 7.5 mmol/L (ref)	1	.93
≥ 7.5 mmol/L	1.04 (0.48–2.24)	
Postoperative renal impairment		
GFR ≥ 45 ml/min/1.73 m (ref)	1	.001
GFR < 45 ml/min/1.73 m2	3.92 (1.77–8.95)	
CRP levels		
CRP < 150 (ref)	1	.06
CRP ≥ 150	2.00 (0.97–4.09)	
Leucocyte blood count		
< 15.0 10^9/l (ref)	1	.026
≥ 15.0 10^9/l	2.28 (1.10–4.70)	
Complications		
CDC < 3 (ref)	1	.001
CDC ≥ 3	2.84 (1.50–5.35)	

Values in parentheses are percentages unless indicated otherwise. OR: odds ratio; CI: confidence interval; GFR: glomerular filtration rate; CRP: C-reactive protein; CDC: Clavien-Dindo classification of surgical complications; * self-reported daily average.

Type of operation was not associated with POD except for patients who underwent a HIPEC procedure who had a 2-fold increase in risk for developing

POD. In 4 patients early signs of dementia were suspected and documented. None of these patients developed POD.

Variables included as potential risk factors ($P < .1$) for POD in multivariate analyses were age, ASA classification, blood transfusion, history of psychiatric disease, history of cerebrovascular disease, postoperative pain management, postoperative renal impairment, CRP levels, leucocyte blood count, and postoperative complications. Adjusted ORs were calculated for these variables (Table 3).

Table 3 Risk factors for POD; results of multivariate analysis

Candidate predictor variable	OR (95% CI)	overall P value
Age (y)		
< 70 (ref)	1	.004
70–80	0.86 (0.37 – 1.98)	
> 80	4.01 (1.55 – 10.37)	
ASA classification		
I/II (ref)	1	.75
III/IV	0.88 (0.41 – 1.90)	
History of psychiatric disease		
No (ref)	1	.02
Yes	8.38 (1.50 – 46.82)	
History of cerebrovascular disease		
No (ref)	1	.10
Yes	2.45 (0.85 – 7.06)	
Transfusion		
No (ref)	1	.03
Yes	2.37 (1.11 – 5.06)	
Postoperative pain management		
Epidural anesthesia (ref)	1	.21
Opioid medication	1.66 (0.76 – 3.63)	
Postoperative renal impairment		
GFR ≥ 45 ml/min/1.73 m (ref)	1	.39
GFR < 45 ml/min/1.73 m2	1.58 (0.56 – 4.40)	

Table 3 Continued

Candidate predictor variable	OR (95% CI)	overall P value
CRP levels		
CRP < 150 (ref)	1	.49
CRP ≥ 150	1.38 (0.54 – 3.56)	
Leucocyte blood count		
< 15.0 10^9/l (ref)	1	.63
≥ 15.0 10^9/l	1.23 (0.53 – 2.89)	
Complications		
CDC < 3 (ref)	1	.06
CDC ≥ 3	2.05 (0.97 – 4.36)	

Values in parentheses are percentages unless indicated otherwise. OR: odds ratio; CI: confidence interval; GFR: glomerular filtration rate; CRP: C-reactive protein; CDC: Clavien-Dindo classification of surgical complications.

Age, history of psychiatric disease, and transfusion were found to be strong independent risk factors for the occurrence of POD. The strongest independent risk factor for POD was found to be a history of psychiatric disease (OR 8.38, 95% confidence interval [CI] 1.50–46.82). In 7 out of 8 cases, a history of psychiatric disease consisted of ≥ 1 episode of depression. For age, the adjusted OR for POD was 4.01 (95% CI, 1.55–10.37) in patients in the highest age group compared with the baseline group. In the group of patients that received perioperative blood transfusion, the OR to develop POD was 2.37 (95% CI, 1.11–5.06), compared to those who did not receive transfusion. When corrected for the occurrence of serious/major complications, increased levels of CRP and leucocyte blood count demonstrated a significant decrease in ORs compared with univariate analyses. Although not significant in multivariate analyses ($P > .05$), history of cerebrovascular disease and perioperative pain management also appeared to be related to POD.

Sensitivity analysis

Repeating the analysis by using only cases with complete data yielded comparable results. Greater age, perioperative blood transfusion, and a history of psychiatric disease were independent risk factors for the occurrence of POD (OR 3.88, 95% CI, 1.49–10.08; OR 2.20, 95% CI, 1.02–4.75; and OR 7.66, 95% CI, 1.40–42.10, respectively).

DISCUSSION

In the present study, 10% of patients undergoing operation for colorectal cancer developed delirium during the postoperative period. Postoperative mortality was found to be greater in patients that developed POD. In-hospital mortality was 8.9% in patients with POD and 3.6% in patients who did not develop POD (*P* = .09). Furthermore, POD was associated with longer admission to the ICU and longer HLOS. Various potential risk factors for POD were identified in univariate analysis, including age, history of psychiatric disease, history of cerebrovascular disease, ASA classification, perioperative transfusion, postoperative pain management, postoperative renal impairment, CRP levels, and leucocyte blood count. The strongest independent risk factors for POD were history of psychiatric disease, age, and perioperative transfusion.

Reported incidences of POD after major gastrointestinal operation vary widely across the literature, ranging from 10% up to 60%[8-10,12,20,21]. In the specific subpopulation of patients undergoing colorectal operation for malignancy, considerably less research has been done on POD and its risk factors. In this specific group of patients, POD incidences varying from 10-35%[8-10,22] have been reported.

Compared with these studies, our results demonstrate a relatively low incidence of POD (10%). This may be partly due to the inclusion of relatively younger patients compared with other studies. The median age was 67 years in our population, while median age was 72 years in the population described by Mangnall et al[9] and 88 years in the population investigated by Brouquet et al[8]. In those studies, the reported incidence of POD was considerably greater compared with our results (35% and 24% respectively).

Another explanation for the relatively low incidence of POD might be implementation of more preventative measures in recent years at our hospital. Well before the start of our study, DOS scores were introduced and a standardized prevention strategy became available. This strategy consisted of promoting orientation, increasing attention toward nutritional needs, promoting

mobility, and when necessary providing visual and hearing aids. Proactive geriatric consultation might have also further reduced the risk of POD.

As demonstrated by the present study and previous research, POD is associated with the development of other postoperative complications and an increased risk of admission to a nursing home, which may lead to increased morbidity and mortality in this patient group[3,8,9,11]. Not surprisingly, POD has been associated with longer hospital stay and higher costs[11]. In the long term, delirium may accelerate cognitive decline in elderly patients[23]. These potential consequences of delirium warrant the identification of predictors, as proactive geriatric consultation in combination with prophylactic, low-dose haloperidol may reduce the incidence and severity of POD[24].

Consistent with other studies, the ASA score was found to be positively associated with POD[8-10]. Patients with an ASA score of 3 or 4 had a greater risk of POD in univariate analyses. Comorbidity reflected by the Charlson comorbidity index was also found to be positively associated with POD in univariate analysis. In a population of elderly patients, the presence of multiple comorbidities has been associated with increased risk for developing delirium, even in the absence of operation[11]. Our findings together with those from the literature suggest that multiple comorbidities and a related impaired physical condition increase vulnerability for POD in elderly patients undergoing operation for colorectal cancer.

The strongest, independent risk factor identified in our study was a history of psychiatric disease. When looking in more detail at this patient group, we noticed that most patients had ≥ 1 episode of depression (7 out of 8). Although the pathophysiology linking POD and depression in unclear, many studies have identified depression as an independent risk factor for POD[25]. Furthermore, POD in patients with a history of depressive disorder is associated with a longer duration of POD and incomplete recovery compared with preoperative functioning[26,27].

Because of the known relationship between intraoperative blood loss and POD,[12,13] we investigated the role of a decrease in postoperative hemoglobin levels. We chose this parameter as a proxy for peroperative blood loss. In contrast to previous studies, a decrease in hemoglobin levels was not found to be significant. However, we did establish a strong connection between POD and perioperative transfusion. In the study published by Brouquet et al, a similar association was found between POD and perioperative transfusion[8]. Although blood transfusions are usually triggered by decreased hemoglobin levels, we did not find a connection between POD and decreased hemoglobin itself. This might indicate that the transfusion of red blood cells increases the risk of POD by itself through mechanisms currently unknown.

Adequate postoperative pain control reduces stress and has a beneficial effect on the postoperative trajectory. Not all analgesics appear to be equally suitable for postoperative use in the elderly. Several studies have identified an association between POD and the administration of meperidine or tramadol in the postoperative period[8,28]. Considerably less research has been done on the relation between POD and mode of administration. To our knowledge, 2 randomized, controlled trials tested the effect of administration mode on POD occurrence and recovery after major abdominal operation in the elderly[29,30]. Both studies failed to demonstrate an effect on the occurrence of POD. By contrast, our results demonstrate a small but beneficial effect of epidural analgesia. As our results differ from previous studies, further research seems warranted to establish whether subgroups might benefit from epidural analgesia with respect to POD.

Preoperative alcohol abuse and POD are known risk factors for POD[22]. Postoperative delirium due to withdrawal from alcohol (delirium tremens) is associated with considerable morbidity and mortality[31]. It also requires supportive measures and specific pharmacologic treatment. For these reasons, it is important to recognize patients at risk at an early stage and implement preventative measures. Our study also detected an increased risk for POD in patients with a history of or current alcohol abuse. This connection was not significant in univariate analyses though. A possible explanation for the

absence of statistical significance might be the instigation of preventative measures during preoperative workup. Furthermore, alcohol consumption was documented using a questionnaire during preoperative consultation by the anesthesiologist, which probably led to an underestimation of actual alcohol consumption.

Despite the many studies on the pathogenesis of POD, the underlying biochemical mechanisms are not yet fully understood[32]. One of the hypotheses is that systemic inflammation, as a response to operative trauma, causes diffuse microcirculatory impairment resulting in neuroinflammation, which in turn may lead to POD[14,15]. In our study, we found the elevated inflammatory marker CRP in the postoperative period to be positively related to POD in univariate analysis. The exact nature of the complex relation between aging, inflammatory response to operation, development of other complications, and POD remains to be determined.

The present study has a few limitations. First, since POD is characterized by fluctuating symptoms, this might have resulted in missed cases. Second, even though this was a prospective study, several known risk factors (i.e. preoperative mini-mental state examination, history of encephalopathy, data on individual support systems, living arrangements, and private versus semiprivate ward hospital rooms) were not documented in the study and could not be retrieved retrospectively from the hospital records. Information on preoperative alcohol consumption and the use of chronic pain medication were recorded during preoperative consultation by the anesthesiologist. For patients requiring emergency operation, these parameters may be underreported. In general, completeness of the data was reasonable; only 6 parameters revealed having missing data. We could not establish a relation between the outcome variable POD and the occurrence of missing data. For this reason, we found it valid to use a data imputation method, thereby increasing our statistical power.

In conclusion, this prospective study shows that POD is a frequently encountered complication in patients undergoing colorectal operation for

malignant disease of the colon and rectum. The present study is based on a homogeneous population of patients who underwent major colorectal operation for malignant disease and explores the relation between POD and a number of potential risk factors. By identifying high-risk patients, preventive measures might be undertaken. The high mortality and morbidity rates associated with POD warrant implementation of preventive and treatment strategies, especially in high-risk patients.

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CHAPTER 6

Predictive performance of TPA testing for recurrent disease during follow-up after curative intent surgery for colorectal carcinoma

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ABSTRACT

Background: The aim of the present study was to investigate the predictive performance of serial tissue polypeptide antigen (TPA) testing after curative intent resection for detection of recurrence of colorectal malignancy.

Methods: Serum samples were obtained in 572 patients from three different hospitals during follow-up after surgery. Test characteristics of serial TPA testing were assessed using a cut-off value of 75 U/L. The relation with American Joint Committee on Cancer stage and the potential additive value of tissue polypeptide antigen testing upon standard carcinoembryonic antigen (CEA) testing were investigated.

Results: The area under the receiver operating characteristic curve of TPA for recurrent disease was 0.70, indicating marginal usefulness as a predictive test. Forty percent of cases that were detected by CEA testing would have been missed by TPA testing alone, whilst most cases missed by CEA were also not detected by TPA testing. In the subpopulation of patients with stage III disease predictive performance was good (area under the curve 0.92 within 30 days of diagnosing recurrent disease). In this group of patients, 86% of cases that were detected by CEA were also detected by TPA.

Conclusion: Overall, TPA is a relatively poor predictor for recurrent disease during follow-up. When looking at the specific subpopulation of patients with stage III disease predictive performance of TPA was good. However, TPA testing was not found to be superior to CEA testing in this specific subpopulation.

INTRODUCTION

Post treatment surveillance is recommended for patients who have undergone surgery with a curative-intent for colorectal cancer. The purpose is to early identify recurrent disease that can be cured by surgical intervention, and to screen for a potential second primary cancer or pre-cancerous adenomatous polyps. For this purpose, a wide variety of surveillance strategies have been described [1]. Most of these strategies include the use of tumor markers during follow-up.

For colorectal cancer three types of tumor markers can be identified, roughly speaking: proteins such as carcinoembryonic antigen (CEA), membrane associated glycoproteins like CA 19-9 and CA 242, and cytokeratins, like tissue polypeptide antigen (TPA). The only commonly used laboratory test to detect recurrent colorectal cancer is CEA. This test has been described extensively with regard to its value during follow-up after treatment for colorectal carcinoma [2-5]. Most guidelines advocate the use of serum CEA testing during the first 3 years after surgical resection making CEA testing an established part of standard follow-up [6,7]. Although many patients with recurrent disease have elevated levels of CEA, not all case can be detected by merely looking at absolute CEA values [8-10]. By intensifying the frequency of CEA measurements during follow-up and looking at a relative rise in CEA, rather than absolute values, detection of disease recurrence is improved [11]. Further improvement of detection of disease might be through determination of additional serum tumor markers during follow-up.

A preceding review of the literature showed that TPA was able to detect recurrent disease in colorectal cancer [12]. However, studies are sparse and mostly focused on prognostic value [13-15] instead of test performance during follow-up. The limited studies on actual predictive value during follow-up, demonstrate considerable differences in test performance, with sensitivities ranging between 34% and 76% [16,17].

Because of the sparse amount of information available with regard to the value of TPA testing during follow-up and the potential benefit of detecting disease recurrence at an early stage, we wanted to investigate the predictive performance of serial TPA measurements for the detection of recurrent disease during follow-up. Furthermore, we wanted to explore whether TPA might offer additional predictive value to standard CEA testing. These research questions were investigated in a specific population of patients that were included in a multicenter clinical trial on follow-up strategies after curative intent surgery for colorectal carcinoma.

MATERIALS AND METHODS

This study was part of a larger encompassing multicenter trial on follow-up after curative treatment for colorectal cancer; the CEA-watch (Netherlands Trial Register 2182) [11]. For a detailed description of this study and its design, we refer to the methods of Zhan et al.[18]. To summarise, in the encompassing study, data were collected in 11 Dutch hospitals with regard to CEA as a marker for recurrent disease. After initial treatment patients were followed-up according to a conventional follow-up schedule. In this stepped-wedge designed study, participating hospitals changed their follow-up schedule to a more intensified protocol [18]. In the conventional schedule, patients were followed-up according to the Dutch guidelines, consisting of 3- or 6-monthly CEA measurements starting 3 months after initial treatment and yearly medical consultation with routine imaging of chest and abdomen (www.oncoline.nl, guideline on colorectal carcinoma, version 3.0). After switching to the intensified protocol, CEA monitoring was done bimonthly. Additional imaging was based on a dynamic threshold rather than looking at absolute values. During follow-up, a total of 2338 study serum samples were collected in 572 participating patients. 146 (26%) patients directly entered the intensified follow-up protocol whilst 426 (74%) patients initially entered the conventional protocol and switched over to the more intensified protocol during the study period. Median follow-up with TPA testing was 13 months. Per patient, a median of four study samples were collected.

Upon inclusion in this study patients were made aware of their participation and an informed consent was obtained. The study received approval of the Ethical Review Board of the University Medical Center Groningen (UMCG) and the Local Ethics Committees of participating centers. Patient data were processed and stored according to the declaration of Helsinki - Ethical principles for medical research involving human subjects.

Patients

In the presented study additional serum samples were collected from July 2011 to December 2012, in three of the participating hospitals. Consecutive patients that underwent R0 resection because of a colorectal cancer (American Joint Committee on Cancer [AJCC] stage I - III), from 2007 to 2012, were included in the study. Initial diagnosis was confirmed with histology and evidence of distant metastatic disease was excluded with additional imaging of liver and thorax. Before surgery all patients were evaluated by an anesthesiologist to determine whether they were fit for major abdominal surgery. According to current treatment standards (http://www.oncoline.nl/colorectaalcarcinoom), some of the patients with rectal cancer underwent neoadjuvant chemoradiotherapy (131 out of 218).

Data collected and handling

Data were prospectively collected with regard to demographic characteristics, location of the primary tumor, procedure performed, initial tumor staging according to the AJCC.

Blood samples were drawn according to standard procedures. Within 2 h after collection, but after coagulation, samples were centrifuged at 1400 *g* for 10 min. Serum was aliquoted and stored at -80 ℃ during the study period. Serum concentrations were quantified using the LIAISON TPA-M automated chemiluminesce immunoassay (Diasorin, Sallugia, Italy). Results exceeding >4000 ng/L were rerun in dilution. Ninety-five percent of healthy men and women were found to have TPA® values below 75 U/L (according to manufacturer, Kit Insert). Intra-assay variation and inter-assay variation

ranges between 3.1% – 3.9% and 4.9%-8%, respectively for levels ranging from 83 – 760 U/L. Analytical and functional sensitivity was <3 U/L and <9 U/L, respectively (data manufacturer, Kit Insert). Trueness was tested by the manufacturer using recovery and dilution tests.

CEA was analysed using a Chemiluminescent Microparticle immuno assay (CMIA) on the Architect i2000SR system (Abbott Laboratories. Abbott Park, Illinois, USA). The assay is standardized against WHO 1ste IS 73/601 for CEA. Results exceeding >1500 µg/L were rerun in dilution. Reference ranges for CEA were established according to CSLI protocol EP28-A, normal values ranging between 0.5-5 µg/L, for smokers values <10 µg/L were considered as normal (personal data Laboratory). Intra-assay variation and inter-assay variation ranges between 2.1% – 3.6 % and 2.7%-4.0 %, respectively for levels ranging from 5 µg/L to 99.5 µg/L (validation data Laboratory, according to CSLI EP5). Analytical sensitivity was < 0.5µg/L (data manufacturer, Kit Insert), and functional sensitivity was not investigated. For CEA, a dynamic threshold was used; a consecutive rise of 20% with CEA value >2.5 ng/mL was considered abnormal.

Statistical analyses

The primary outcome variable was recurrent disease after a R0 resection for primary colorectal malignancy. When recurrent disease was suspected based on either symptoms, elevated tumor markers or routine imaging, a conformation of disease recurrence was required by either radiology or histology. The date of recurrence was defined as the date of disease confirmation by one of these modalities. Recurrence rates were compared between hospitals using the χ^2-test statistic.

Sensitivity and specificity of TPA were assessed within 30 days of diagnosis of recurrent disease. Based on tumor biology, a gradual increase in tumor marker levels can be expected in the period before recurrent disease manifestation. This phenomenon was investigated by determining median TPA values at 60 and 90 days before diagnosis. Predictive performance using continuous

TPA value was assessed by calculating the area under the receiver operating characteristic (AUC ROC) curve [19]. The predictive performance of TPA was also assessed in relation to location of disease recurrence and in relation to AJCC stage. After assessment of predictive performance, we explored the additional value of TPA to CEA compared to CEA alone. First, we investigated how many cases that were detected by a rise in CEA would have been missed by TPA. After this, we investigated whether there were cases that were missed by CEA that could have been detected by TPA.

All calculations were performed using Statistical Analysis System (SAS) version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 572 patients were included in the study. Table 1 demonstrates the baseline characteristics of the study population.

Table 1 Patient, tumor and treatment characteristics (n=572)

Characteristics	
Age, years	
Median	68
Range	34–88
Gender	
Male	350 (61%)
Female	222 (39%)
AJCC, n (%)	
I	152 (27%)
II	230 (40%)
III	190 (33%)
Mean pre-treatment CEA	10.4 ng/mL
Initial surgical treatment, n (%)	
Right sided hemicolectomy	148 (26%)
Left sided hemicolectomy	39 (7%)
Low anterior/ sigmoid resection	253 (44%)
Abdominoperineal resection	75 (13%)
Other	57 (10%)

One patient deceased during follow-up. At the time of death, there was no evidence of metastatic disease. During follow-up, a total of 46 (8%) recurrences

of disease were diagnosed. Distant metastasis were observed in the liver (12 cases), lungs (6 cases) or other sites (9 cases). Local recurrent disease was observed in 12 patients. A minority of patients were found to have metastatic disease at multiple locations at the time of diagnosis (7 cases). Recurrence rates did not differ significantly between participating hospitals ($p = 0.24$). Patients with recurrent disease demonstrated higher serum levels of TPA. Median TPA was 92 U/L (IQR, 36 - 147), 30 days before detection of disease compared to a median TPA value of 48 U/L (IQR, 32 - 66) in the group of patients that did not develop recurrent disease during follow-up (Kolmogorov-Smirnov test, p-value=0.01).

Table 2 demonstrates the test characteristics of TPA for detecting recurrent disease for a fixed cut-off value of 75 U/L.

Table 2 Test characteristics of median TPA within 30 days to diagnosis for the detection of recurrent disease stratified for AJCC stage

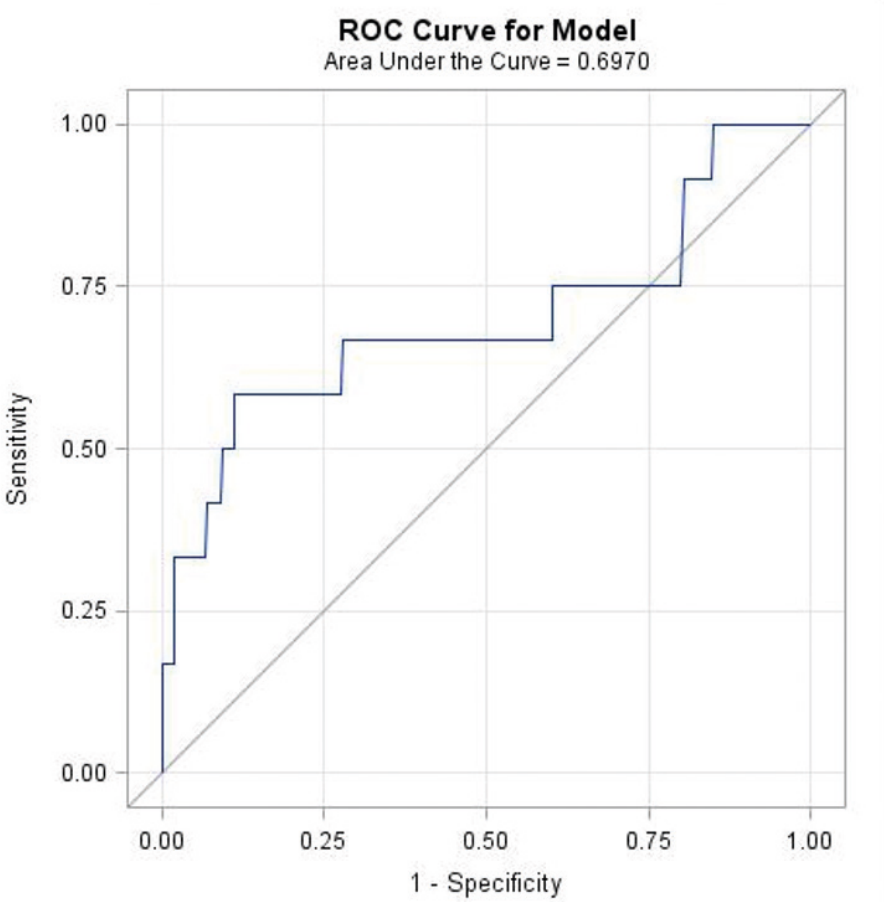
	TPA	No recurrence of disease (specificity)	Recurrent disease (sensitivity)
Overall			
	< 75 U/L	430 (81.75%)	5
	≥ 75 U/L	96	7 (58.33%)
Stratified for AJCC stage			
I	< 75 U/L	120 (82.76%)	-
	≥ 75 U/L	25	-
II	< 75 U/L	176 (81.86%)	4
	≥ 75 U/L	39	0 (0)
III	< 75 U/L	134 (80.72%)	1
	≥ 75 U/L	32	7 (87.50%)

Values in parentheses represent test characteristics; in the group without recurrent disease test specificity and in the group with recurrent disease test sensitivity are displayed

Test sensitivities are shown for the whole group and stratified to AJCC stage. As can be deduced from the table, overall sensitivity was 58% within 30 days to diagnosis. When looking at the relation between test performance and AJCC stage, TPA was found to be more sensitive for patients with stage III disease (sensitivity 87.5%). Only two patients with an initial AJCC stage I disease were diagnosed with recurrent disease. Therefore, no reliable estimates of test

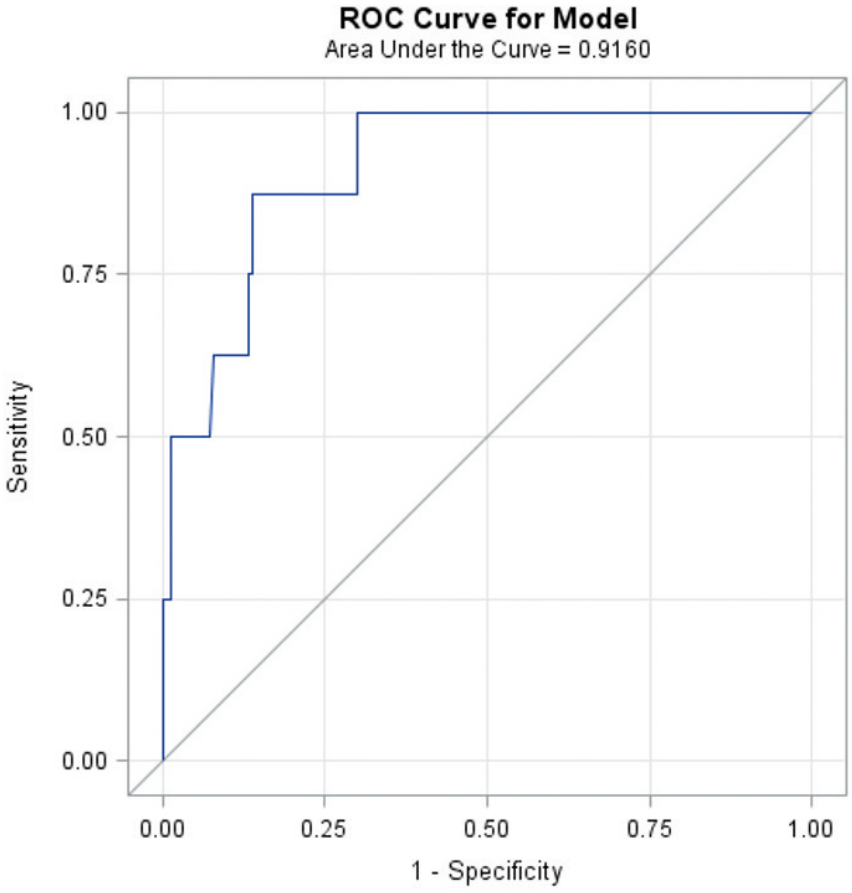
characteristics could be provided for this group of patients. A similar relation can be observed when looking at continuous TPA value as is demonstrated in Figure 1.

Figure 1 ROC curve of TPA for detection of recurrent disease within 30 days to diagnosis



The AUC of TPA was 0.70 for the whole population, which increased to 0.92 for patients with stage III disease (Figure 2).

Figure 2 ROC curve of TPA for detection of recurrent disease within 30 days to diagnosis for patients with AJCC stage III disease.



Patients that were found to have recurrent disease at multiple locations, demonstrated a median TPA of 149 U/L within 30-days to diagnosis. Median TPA was significantly higher in this group compared to the recurrent disease at a single location group (median, 149.00 vs. 41.40, Kolmogorov-Smirnov test p-value=0.0275).

Assessment of the relation between CEA, TPA and the detection of recurrent disease revealed that within 30 days to diagnosis 4 of 10 cases that were detected by a rise in CEA would have been missed by TPA alone. There was only one case that was not detected by a rise in CEA but could have been detected by TPA testing (TPA>75 U/L). Fortunately this case was detected by routine imaging. When doing the same analysis for the subgroup of patients

with stage III disease, fewer cases are missed; six out of seven patients initially treated for stage III disease that develop recurrent disease that was detected by a rise in CEA also demonstrate a rise in TPA within 30 days to diagnosis. Within this subpopulation of patients only one case would have been missed by TPA testing alone. Furthermore, in this group one case was detected by routine imaging that was not detected by CEA testing but would have been detected by TPA testing.

Finally, we explored the effect of increasing the time interval to diagnosis of recurrent disease. When expanding the time window to 60 days, median TPA decreased from 92U/L to 64U/L (IQR, 41 - 105) in the recurrent disease group. Median TPA remained significantly higher when increasing the time intervals to 90 days (69U/L (IQR, 36 - 124) from 48 days (IQR, 32 - 66) in the no-disease group, Kolmogorov-Smirnov test p-value=0.004). Correspondingly, overall test sensitivity decreased to 45% in the overall group and 61% in the stage III disease subpopulation. This is reflected by a similar decrease of the AUC when looking at continuous TPA value. The AUC decreased to 0.66 overall and 0.80 for the stage III group.

DISCUSSION

This study shows that, overall, TPA is a relatively poor predictor for recurrent disease during follow-up after curative intent surgery for colorectal carcinoma (sensitivity 58%; AUC ROC, 0.70 within 30 days to diagnosis). Test characteristics were found to be inversely related to time to diagnosis; median TPA was significantly higher closer to the moment of diagnosis of recurrent disease. When looking at the specific subpopulation of patients with AJCC stage III disease specificity remained the same but sensitivity and AUC demonstrated a plain improvement (sensitivity 87.5%, AUC 0.92). Furthermore, median TPA was significantly higher in patients that had recurrent disease at multiple locations compared to patients with recurrent disease at a single location. These findings appear to indicate that TPA is better in detecting recurrent disease after initial treatment for the higher tumor stages.

The notion that disease stage influences test performance for both the diagnosis of primary disease and the detection of disease recurrence, is supported by TPAs biochemical characteristics. TPA is a circulating complex of cytokeratins 8, 18 and 19. These cytokeratins are characteristic for normal endothelium. During malignant transformation the expression of cytokeratins is usually continued. When cells divide more frequently, the probability of cell rupture becomes higher. By releasing their content, ruptured cells may increase serum concentration of cytokeratins, resulting in a correlation between cell proliferation and TPA. Proliferative tumor markers like TPA express proliferative activity and therefore reflect tumor aggressiveness. Immunohistochemical analysis has demonstrated a greater incidence of recurrence and shorter disease-free interval and survival in colorectal tumors that expressed TPA [20]. Furthermore, in patients with metastatic colorectal cancer treated with combination chemotherapy, higher levels of TPA are associated with poor response to therapy and prognosis [21,22]. A similar association has been described in patients after liver surgery or radiofrequency ablation for colorectal liver metastases. In this group of patients decreased levels of TPA were associated with increased survival and disease free interval [23].

When looking at cases that were missed by CEA, we could not establish a clear additional benefit of TPA testing. Only one case that was missed by CEA testing, would have been detected by TPA testing whilst 40% of cases that were detected by CEA testing, would have been missed by TPA testing alone, indicating that, though not formally tested, CEA is a stronger marker than TPA for prediction of disease recurrence.

Unlike the predictive performance of serial CEA testing during follow-up, TPA has not been described extensively for this specific purpose. Fernandes et al. investigated the value of TPA testing (cut-off value 72 U/L) after curative resection for colorectal cancer. In this study a sensitivity of 76% and a specificity of 72% were reported for the detection of recurrent disease [16]. A possible explanation for this higher sensitivity compared to our results, could be the inclusion of relatively more stage III/IV patients in their study population (58% compared to 33% in the presented study), and their relatively lower cut-off value

of 72U/L. Nicolini et al. investigated an intensive follow-up strategy with the use of a tumor marker panel including CEA and TPA [17]. In this study the reported overall sensitivity of TPA (cut-off value 95 U/L) was considerably lower, namely 34%. Interestingly, in this study the percentage of patients with stage III/IV disease was also lower compared to the study published by Fernandes et al. As mentioned before, in our study test sensitivity was found to increase with initial AJCC tumor stage. The findings from the literature seem to agree with our finding that sensitivity of TPA for detection of disease recurrence increases with initial tumor stage.

The present study has several limitations. First; TPA testing was not done during the entire course of standard postoperative surveillance (5 years). In contrast; CEA values were obtained during this whole period including pre-treatment levels. Because we described test characteristics during the first period of follow-up we cannot say for shore whether predictive performance would have remained stable during the entire follow-up period. Second; TPA values were not involved in actual clinical decision making and the decision to take perform extra CEA testing was based on a relative increase in CEA. In these cases also extra TPA serum samples were obtained. This method of collecting samples introduced a selection bias in such a way that might have favored CEA test characteristics compared to TPA. For these reasons, a direct comparison between test performance of CEA and TPA would provide biased results. Therefore, we choose not to do any statistical testing on differences in test characteristics.

One of the advantages of this study is that it was embedded in a larger randomized controlled trial which ensured a prospective data and good quality collection and storage according to a strict study protocol. Additionally, compared to other studies on the performance of TPA during follow-up, our study describes a relatively large population of well documented patients.

In conclusion, our findings indicate that TPA testing is a mediocre test for the detection of recurrent disease after curative intent surgery for colorectal

carcinoma. With regard to CEA we did not establish an evident additional benefit of TPA testing during follow-up. In patients with stage III disease, test performance was considerably better but did no demonstrate improved detection of recurrent disease compared to CEA.

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CHAPTER 7

General discussion and future perspectives

Currently, colorectal cancer is the third most frequently diagnosed type of cancer in the Netherlands. Annually, approximately 14,000 patients are diagnosed with colorectal cancer in the Netherlands. Roughly one third of these patients is diagnosed with rectal cancer. Since the 1990s both the incidence rate and survival of colorectal cancer are gradually increasing. However, despite of a gradual increase in survival, mortality caused by colorectal cancer remains significant (crude mortality rate in 2017 of 29.43)[1]. Over the coming years, the number of patients diagnosed with colorectal cancer is expected to increase due to a further increase of the incidence rate and aging of the current population. Because of these aspects, colorectal cancer places a significant burden on Dutch healthcare system and will continue to do so in the near future.

Although colorectal surgery has been described since ancient times, the most significant developments have taken place during the last 100 years. During this period colorectal cancer treatment changed from a major surgical procedure with high mortality and morbidity to a multimodality treatment strategy in which the trend appears to be towards individualized treatment strategies that consist of neoadjuvant treatment followed by a less invasive mostly sphincter preserving surgical procedure. Neoadjuvant chemoradiotherapy (nCRT) has become an important part of this treatment resulting in a significant percentage of patients with a pathologic complete response (pCR). Today, for patients diagnosed with a superficial tumor, local excision through Transanal Endoscopic Microsurgery (TEM), has been proven to be a viable treatment option [2]. Furthermore, the watchful wait strategy has also been established as a feasible and safe treatment option in those patients that appear to have a complete response.

All of the available treatment options and strategies are associated with different advantages and risks. To further complicate decision making, based on a patients baseline characteristics, the risks and advantages of a single treatment option differ between individual patients. These aspects complicate clinical decision making and ask for an individualized approach. The last decades there has been a trend in patient tailored treatment strategies in which patient specific risks and preferences are weighted. In order to do so, it is important to make a reliable estimation of procedure related risks and benefits. The aim of this

thesis was to aid clinical decision making by investigating potential predictors of several clinical relevant events during the course of colorectal cancer treatment.

In **Chapter 2**, several known and unknown potential predictors of pCR after nCRT for rectal cancer are investigated. The association between a pre-determined set of potential predictors and pCR after nCRT was investigated in a nationwide and unselected cohort. A total of 6,444 consecutive patients that underwent surgical treatment for rectal cancer were included in the study. Overall pCR was observed in 1,010 patients (15.7%). Both pre-treatment clinical tumor stage and signs of obstruction were independently associated with pCR. Nodal stage and presence of metastatic disease, decreased the probability of a pCR significantly. The best response rate was observed in patients diagnosed with a non-obstructive, well/moderately differentiated adenocarcinoma of the lower rectum with no clinical apparent nodal or distant metastatic disease (pCR ratio 18.8%). The pCR rate improved further when surgical treatment was performed between 16 and 24 weeks post nCRT (pCR, ratio 22%). The percentage of patients demonstrating pCR decreased in case of symptoms of pre-treatment obstruction or poorly differentiated tumors (pCR ratio of 11.8% and 6.7%, respectively). Furthermore, pCR was confirmed to be related to histologic subtype (in favour of adenocarcinoma), distance to the anal verge and ASA classification (in favour of the lower ASA subgroups). After having investigated potential predictors for pCR we studied the relation between pCR and surgical morbidity. The results of this study are demonstrated in **Chapter 3**. The effect of pCR on post-operative surgical morbidity was investigated in a nationwide and unselected cohort of patients that received nCRT before undergoing resection of a primary tumor of the rectum. Between 2009 and 2017, 8,003 patients underwent nCRT and surgical resection according to TME principles in the Netherlands. These patients were included is the study population. Data were stratified into patients who underwent resection with the creation of a primary anastomosis (N=3,472) and permanent stoma procedures (N=4,531). In the group of patients with a primary anastomosis, more surgical complications and anastomotic leakage were observed when pCR was present compared to no pCR ($OR_{adjusted}$: 1.56, 95% CI: 1.25-1.95; $OR_{adjusted}$: 1.49, 95% CI: 1.04-2.15, respectively). In the permanent stoma group,

surgical complications were not significantly more often observed when pCR was present ($OR_{adjusted}$: 1.15, 95% CI: 0.91-1.47). We concluded that; patients with a primary anastomosis may have an increased risk on anastomotic leakage (and other surgical complications) when pCR is present, where this is not the case for patients without a primary anastomosis.

In **Chapter 4**, the development and external validation of a clinical prediction model for in-hospital mortality after colorectal surgery is described (the Identification of Risk after Colorectal Surgery (IRCS) score). The model was developed in a population of patients that underwent elective or emergency colorectal surgery from 1990 to 2005, at the Zaandam Medical Centre, the Netherlands. The model was validated in a population of patients that underwent colorectal surgery from 2005 to 2011, in Barcelona, Spain. In our model development population we identified the strongest predictors of in-hospital mortality; emergency surgery (OR=6.7, 95%-CI: 4.7-9.5), tumor stage (OR=3.2, 95%-CI: 2.8-4.6), age (OR=13.1, 95%-CI: 6.6-26.0) pulmonary failure (OR=4.9, 95%-CI: 3.3 – 7.1) and cardiac failure (OR=3.7, 95%-CI: 2.6-5.3). These parameters were used to create a simplified scoring system; the IRCS score. The model demonstrated a predictive performance of 0.83 area under the receiver operating characteristic (AUC ROC) curve (95% C.I.; 0.79 – 0.87) in the validation population. In this population the AUC ROC of the CR-POSSUM score was 0.76 (95% C.I.; 0.71 – 0.81). Based on the AUC ROCs it was concluded that the IRCS score is a good predictor of in-hospital mortality after colorectal surgery in both study cohorts despite of the relatively low number of model parameters. Furthermore, the study identified the most important predictors of surgical mortality in the model creation cohort.

Chapter 5 describes the identification of independent risk factors for postoperative delirium (POD) among patients that underwent elective or emergency surgery because of malignancy of the colon, sigmoid or rectum between 2009 and 2012 in the University Medical Center Groningen, the Netherlands. During this period 436 patients were included in the study. Postoperative delirium was observed in 45 (10.3%) patients. Patients with a delirium had a higher in-hospital mortality rate (8.9% versus 3.6%, P=0.09),

spent more days at the Intensive Care Unit and had a longer total hospital stay. Independent risk factors were: history of psychiatric disease (odds ratio 8.38, 95% CI: 1.50–46.82), age (odds ratio 4.01, 95% CI; 1.55–10.37) and perioperative blood transfusion (odds ratio 2.37, 95% CI; 1.11–5.06). The study shows that POD is a frequently encountered complication after colorectal surgery and identified three major independent risk factors for POD that can contribute to risk estimation.

In **Chapter 6** the predictive value of serial tissue polypeptide antigen (TPA) testing after curative intent surgery for the detection of recurrent disease was investigated. For this purpose serum samples were obtained in 572 patients from three different hospitals during follow-up after surgery. The area under the receiver operating characteristic curve of TPA for recurrent disease was 0.70 indicating marginal usefulness as a predictive test. 40% of cases that were detected by CEA testing would have been missed by TPA testing alone, whilst most cases missed by CEA were also not detected by TPA testing. It was concluded that overall, serial TPA testing is a relatively poor predictor for recurrent disease during follow-up.

THIS THESIS IN RELATION TO CURRENT LITERATURE

Recently the results of an international study on watchful wait after nCRT were published [3]. This prospective study included 880 patients with a clinical complete response that were treated with watchful waiting. During follow-up, in a significant percentage of patients regrowth was encountered (2-year cumulative incidence of local regrowth 25.2%). Apparently, despite of modern imaging techniques, it remains difficult to determine which patients are true complete responders after nCRT. Several studies have described potential predictors for pCR after nCRT. However, most studies address a limited number of parameters in a relatively small and selected population. Most parameters that are associated with an improved pCR rate in the study described in **Chapter 2**, are also linked to pCR in other studies (tumor size [4-6], distance to the anal verge [7,8], histologic subtype and time interval between nCRT and surgery [8,9]). The relation between increased tumor size and a decreased probability on pCR seems intuitive. Increasing the length of the time interval between nCRT

and surgery is a somewhat less obvious predictor of an increased probability of pCR. Several previously published studies reported an increased probability on pCR when applying time intervals of over 7-8 weeks compared to shorter intervals [4,10-12]. Our study demonstrated a similar beneficiary effect of time intervals of at least 8 weeks post nCRT on pCR. Based on the results of the study described in **Chapter 2** in combination with previously published studies [4,10-12] it seems likely that increasing the interval from nCRT to surgery increases the pCR rate.

Previously, tumors located closely to the anal verge were reported to be associated with an increased pCR rate [7,8]. Although relatively small and not significant in multivariable analyses, we found a similar relation in our study. In contrast to this finding, other studies have reported no differences in pCR rates related to location [13] or even a higher risk of local recurrence for lower tumors[14]. Based on our study and results from current literature, the effect of tumor location on response grade appears to be small at the least and of little clinical importance as a predictor for pCR.

After having investigated potential predictors of pCR we investigated whether pCR itself is associated with postoperative surgical complications. The study described in Chapter 3 demonstrated a clear association between the occurrence of surgical complications (most important anastomotic leakage) and pCR. We searched the literature in order to assess whether others had described a similar relation between response to nCRT and surgical complications. To our knowledge, four studies have been published on this topic [15-18]. Two of those studies found no differences in terms of postoperative complications between patients with and without pCR [17,18], one study found more complications in the no-pCR group[15] and one study described an increased risk of anastomotic leakage among the patients with histologic regression grade 2 and 3 [16]. Compared to these studies, our study was conducted in by far the largest and unselected nationwide population. Furthermore, compared to the other studies, our study has a systematic approach on how to deal with potential confouders. The literature was searched for parameters that were known to be both associated with pCR and anastomotic leakage without

being in the causal path. One of the parameters that was considered to be an important confounder was time interval from nCRT to surgery. Data from the GRECCAR 6 study suggest that more complications are encountered when the interval between nCRT and surgery is longer [19]. In contrast to this finding, the Stockholm III trial found in their pooled analysis that the risk of postoperative complications was significantly lower after short-course radiotherapy with delay [20]. Regardless of the exact nature of the relation between time interval and surgical morbidity, the parameter was included in the multivariable analyses. Several other variables were also entered into a multivariable model. Despite of adding these variables to our analyses our main finding; the association between pCR and anastomotic leakage, remained significant. Apart from anastomotic leakage, another major postoperative complication that was investigated was POD. Although POD by itself is not directly life threatening, it does occur relatively frequent (reported incidences varying from 10 to 35% [21-24]) and is associated with severe discomfort and other complications that in turn may be related to mortality. While POD may occur in patients of any age, it is particularly common among the elderly [25]. Among frail elderly patients POD has a prevalence of up to 60% after major surgery [26]. With the population ageing, the number of major colorectal surgical procedures on the elderly will continue to increase. The incidence of POD is therefore expected to increase in the coming decades. The potential risk factors for POD that were analyzed in **Chapter 5** were largely selected based on previously published studies. Although many studies had investigated potential predictors for POD after major surgery in general, not many studies have been published that were executed in the specific population of patients undergoing colorectal surgery [22,23]. The risk factors for POD that were identified were largely consistent with other studies; age, history of psychiatric disease, history of cerebrovascular disease, ASA classification, perioperative transfusion, postoperative pain management, and postoperative renal impairment. The strongest independent risk factor that was identified was a history of psychiatric disease. Most of the patients with POD and a history of psychiatric disease had at least one episode of depression in their medical history. This finding is consistent with several studies that have identified a previous episode of depression as an independent risk factor for POD [27]. Furthermore, POD in patients with a history of depressive disorder is associated with a longer duration of POD and incomplete recovery compared

to preoperative functioning [28,29]. In contrast to previous studies, post-operative decrease in hemoglobin levels was not found to be a significant predictor of POD. However, we did establish a strong connection between POD and perioperative transfusion. In the study published by Brouquet et al. a similar association was found between POD and perioperative transfusion [21]. This might indicate that the transfusion of red blood cells increases the risk of POD by itself through mechanisms currently unknown.

Methodological considerations

The studies that are described in **Chapters 2** and **3**, are based on the results of analyses performed in a large, nationwide colorectal database (Dutch ColoRectal Audit (DCRA) database). In this database, data is collected with regard to a variety of process and clinical outcome parameters. Data delivery to DCRA database was made mandatory for all hospitals performing colorectal cancer surgery in the Netherlands by the Dutch Health Care Inspectorate in 2010 and can therefore be considered to be a nationwide database. The main goal of the database is to provide insight in the quality of colorectal cancer surgery in the Netherlands and to detect trends and developments. It was not designed and constructed for one specific research topic. Because of this, the database is not likely to provide data on all relevant parameters for a specific research question. For the study presented in **Chapter 2**, this meant that several potential predictors of pCR were not present in the database and could therefore not be analyzed. This was also the case for the study described in **Chapter 3**; not all potential relevant parameters are included in the DCRA database. Apart from the absence of certain potentially interesting parameters we also observed data to be missing within the database. In these cases a missing value analysis was performed. Fortunately, in both studies there was no relation between absence of data on a certain parameter and the concerning outcome parameter. The missing data was found to be missing at random. With regard to study described in **Chapter 4**, several aspects should be mentioned. The model that is described in this study was developed in a single institution cohort. The data was collected during a relatively long time-frame (1990-2005). As mentioned previously in this thesis, developments in colorectal surgery have been abundant during the past decades. Although the model performs

well in a historic external cohort, this might not be the case in a current cohort of patients in whom patient characteristics, treatment strategies and surgical procedures differ. As mentioned before, surgical treatment has shifted to a more conservative spectrum which by its nature is associated with lower procedure related risks. Similar aspects also apply to the study described in **Chapter 5**. This study was also executed in a patient population from a single institution. This particular population was derived from a tertiary referral center and is therefore not a representative for the "general" surgical population. Also several known risk factors for POD were not documented during the study and could therefore not be analyzed. Compared to the literature, a relatively low incidence of POD was encountered (10%). This might be due to underreporting of POD. Another potential explanation might be the inclusion of relatively younger patients compared to other studies. Another explanation for the relatively low incidence of POD might be implementation of more preventative measures in recent years. Whatever the cause might be, a relation between reporting of POD and the investigated potential predictors seems unlikely. Finally, there are also some methodological aspects of the study on the predictive performance of serial TPA testing, presented in **Chapter 6** that should be mentioned. As explained in **Chapter 6**, the study was embedded in a larger multicenter study on the predictive performance of serial CEA testing strategies. In contrast to the CEA testing during the study, TPA was tested in a smaller subgroup, was not tested before surgical treatment, was in general tested during a shorter postoperative period and did not actually influence whether or not additional imaging or laboratory testing was performed. Because of these aspects, it was not possible to make a direct comparison between TPA and CEA (no statistical testing for difference in predictive performance). Furthermore, since CEA testing directly influenced clinical decision making and TPA testing did not, the current study design does not allow for a valid verdict on a potential additive effect of TPA testing on standard serial CEA testing.

IMPLICATIONS OF THIS THESIS ON CLINICAL PRACTICE

The study described in **chapter 2**, offers several pre-treatment tumor characteristics that are associated with low or high probability of true pCR after nCRT. Pre-treatment assessment of these parameters may aid patient

and physician in the process of determining which treatment strategy to follow. Another important factor in the decision making process at this stage, is the estimation of treatment associated risks. Based on a relatively small cohort study, Horisberger et al. demonstrated an elevated risk on anastomotic leakage when pCR was present [16]. Whatever the cause might be, our nationwide population based study yielded a similar result; a significant higher percentage of anastomotic leakage among patients with a pCR. This finding is relevant when for example trying to decide whether to perform major surgery in a patient with major cardiovascular or pulmonary comorbidity. Especially in high risks sub-groups a complication like anastomotic leakage might have devastating effects. Based on our results (**chapter 3**), sphincter preserving surgery when complete response is present coincides with a significantly higher risks on surgical morbidity. The study underlines the importance of considering alternative treatment strategies other than TME with sphincter preservation when complete response is estimated to be likely.

At the time of publication of the study described in **Chapter 4**, already many surgical risk scoring models and calculators had been developed (CR-POSSUM, ACPGBI Colorectal Cancer Model, ACPGBI Malignant Large Bowel obstruction model, Cleveland Clinic Foundation Colorectal Cancer Model, elderly Colorectal cancer model, Association Française de Chirurgie score and the American College of surgeons risk calculator [30-33]). Compared to these models, the IRCS score consists of relatively few parameters and is easy to calculate. Despite this, the model yielded good predictive performance in the external validation. Although this was one of the main objectives of the study it is questionable whether clinical practise is currently still served best by simplicity. Data acquisition and storage has evolved greatly over the last decades. Processing of complex data and interpretation is changing and appears to become an automated process (see section on Machine Learning).

After having made the decision for colorectal surgery and having undergone the surgical procedure itself, the patient faces several potential complications. As mentioned before, POD is one of those complications that is relatively frequently encountered. Fortunately, precautionary interventions aimed at reducing the

prevalence of delirium have proven to be effective[34]. Especially, when the prior risk of POD is over 30%, these measures appear to be effective [34]. In the study presented in **chapter 5**, we provide the reader with several risk factors that are strongly related to the development of POD after colorectal surgery that are helpful during the allocation of additional resources. Finally, based on the results of the study presented in **chapter 6**, we conclude that serial TPA testing is a relatively poor predictor of recurrent disease. Furthermore, there does not appear to be a clear additive effect of TPA alongside CEA testing.

FUTURE OF PREDICTION MODELS IN COLORECTAL SURGERY

In order to make a proposition about a certain probability on a certain event in a certain population classically a process is used called statistical inference. In this process data is being analyzed in order to deduce the qualities of an underlying probability distribution. Based on sample data, an attempt is made to estimate the probability that the observed event or difference is either related to a certain parameter or one that the observed effect is caused by chance. When attempting to predict probabilities or explain certain phenomena, an inferential data model can be created. These models are basically handcrafted to predict a certain event in a certain (training) dataset. These heuristic models are then assessed for “goodness of fit”; how well does the new model predict an event compared to a presumptive model. This way of modelling is feasible when there is one dataset that is relatively uncomplicated and consists of a reasonably number of potential predictors. When faced with multiple complex datasets that are composed of large numbers of different parameters, the process of classical inferential data modelling becomes difficult.

Today, the amount of data available for clinical research is rapidly increasing. From the moment a patient enters a hospital, data is being collected and stored on a large variety of parameters. For example, patient history, results of biochemical tests and radiographic imaging are documented and stored electronically. Furthermore, in the past decades there has been a trend in an increasing number of nationwide disease specific databases. Most of these databases are being used for the monitoring of differences in treatment

outcome of oncological diseases between different hospitals. For example, for colorectal cancer, data is collected in the Dutch ColoRectal Audit (DCRA, www.dica.nl/dcra) database and since 1991, all results of pathological examination are archived in a nationwide database (*Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief* (PALGA)). Furthermore, in the context of clinical trials, there is also a lot of data collection and storage being conducted in the Netherlands. Like in many fields, data collection on colorectal cancer patients has increased and diversified over the last decades. Data is largely collected electronically and spread across different local and nationwide databases. This large volume of available biomedical data offers a lot of research potential but also a challenge on how to process this data using conventional statistical techniques and come to meaningful individualized risk predictions. Apart from large data volumes, it is well recognized that in the case of a complex disease like cancer, tumor behavior and response to treatment is influenced by far more parameters and interactions then a human mind can process.

In recent years, Machine Learning (ML) has been gaining popularity for the analyses of large datasets. Originally ML was developed from Artificial Intelligence in the 1990s. It is basically the study of how to make "machines" uncover/recognize patterns in data and make future predictions without explicit instructions. In general, ML does not use classic hypothesis testing but instead uses an algorithm to detect patterns in the data. Unlike data mining, ML focusses on predicting events based on previously learned characteristics instead of detecting previously unknown properties in a dataset. For the actual process of developing a prediction model, an algorithm is used. This algorithm may consist of various processes, techniques and models like; decision trees, artificial neural networks and Bayesian networks. One of the interesting aspects of these algorithms is that these can be used to create re-usable frameworks. Thus a single ML framework might be used on different datasets in order to make predictions for different diseases and scenarios.

Since the 1990s, ML is being applied as a prediction tool in an increasing number of fields. Not surprisingly there has been a parallel growth in companies that focus on "big dataset" analyses. Some of these companies have turned

their attention to the development of ML frameworks for healthcare. As a result, ML is becoming a well-accepted analytical tool in healthcare. Especially, in medicine it is becoming a popular tool in the prediction of response to medical treatment of malignancies. For example, for breast cancer several studies have been published that apply ML techniques in order to predict treatment outcome based on genomic data. In contrast, there appears to be a relatively slow entrance of ML for the specific prediction of surgical outcome. In the case of colorectal cancer, little studies have been published that actually use ML for their risk prediction models. Gründner et al. created a model for the prediction of colorectal cancer outcome in which both gene markers and other patient features were combined to predict clinical outcomes[35]. This study nicely illustrates how ML can analyze a complex database and combine different types of parameters in a prediction model. In the near future, we may expect the availability of "big data" sources, large data streams and data processing capacity to increase. As a result of these developments we may expect a parallel increase in the need for methods that are able to analyze large amounts of complex data. Although, analyzing large datasets with ML is being popularized in the last decades, there are some disadvantages and shortcomings that should be mentioned. The datasets that are being used are often designed for a purpose other than research. Compared to the data collected in a clinical trial, there may be an increased risk on for example selection bias[36]. Furthermore, ML predicts events based on past data. Treatment strategies constantly change as do diagnostics, social phenomena and epidemiology. Although, the model may be perfect for risk estimation in a historical cohort exact estimation of future events is impossible [37].

FUTURE OF CLINICAL DECISION MAKING IN COLORECTAL SURGERY

Decision making in healthcare and medicine is increasingly being based on quantifiable data. In general, clinical decisions and practice guidelines are based on the results of statistical analyses of data obtained from retrospective or prospective clinical studies.

Accurate risk estimation does not automatically lead to “good” choices. The potential outcomes of different treatment strategies are usually related with different benefits and harms. When a certain option is clearly related with increased benefits and less harm, the choice is relatively easy. However, sometimes the associated risks and benefits are not so far apart. Furthermore, the “value” that is accredited to a certain outcome may differ between patients. In these situations, a patients personal preferences becomes an important factor. It has been shown that involving patients in decision making results in increased patient satisfaction and adherence to therapy[38].

Shared decision making (SDM) in surgery is especially important when making a choice between surgery and no surgery (for example watchful waiting)[39]. Since surgery is irrevocable and the effects of complications might be permanent, patients may have to deal with reduced quality of life over a prolonged period of time. Based on the growing number of studies being published on SDM, there appears to be an increasing interest of surgeons in this way of decision making. Few studies have been done on SDM in the specific field of colorectal cancer treatment. The studies that have been done report somewhat contradictory results. Beaver et al. reported that the colorectal cancer patients in their study wanted to be well informed and involved in the consultation process but did not necessarily want to use the information they received to make decisions[40]. In another study published by Hirpara et al. patients wanted to be involved but experienced a lack of lack of choice and control in decision-making[41]. Furthermore, this study reported a crucial role of family engagement in the decision making process. Possibly the best form of SDM is also dependent on individual patient characteristics. Although common denominators appear to be; information and involvement during every step of the treatment and involvement of a patients social support system.

In conclusion colorectal cancer is a disease that places a large burden on health care and is expected to continue to do so in the near future. Partly because of an evolving array of potential management strategies its prognosis in improving. The process of determining which management strategy to choose has also been evolving during the past decades. More and more patients are

being actively involved in the decision making process. In order to make a well balanced decision regarding treatment options, both physician and patient require personalized risk estimates of the different treatment options. This thesis provided information on risk factors and predictors of several clinically relevant events during surgical treatment of colorectal cancer.

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7

CHAPTER 8

Nederlandse samenvatting

Dikke darmkanker (coloncarcinoom) en endeldarmkanker (rectumcarcinoom) komen relatief frequent voor in Nederland. Gezamenlijk nemen zij de derde plek in van de meest frequent gediagnosticeerde vormen van kanker. Voor beide tumorsoorten kan worden gesteld dat sinds de jaren negentig zowel het aantal nieuw gestelde diagnoses als de overleving geleidelijk toenemen. In 2014 werd een landelijk screeningsprogramma naar colorectaalcarcinoom (gezamenlijke noemer dikke darm- en endeldarmkanker) ingevoerd. Hierop werd een verdere toename van het aantal nieuwe gevallen van colorectaal carcinoom per jaar (de incidentie) geobserveerd in 2015 en 2016. Sinds 2017 lijkt de incidentie weer te zijn gedaald naar het niveau van voor de introductie van het screeningsprogramma. In 2018 werd in Nederland bij ongeveer 14.000 patiënten de diagnose dikke darm- of endeldarmkanker gesteld. Bij ruwweg één derde van deze groep ging het om endeldarmkanker.

Helaas is ondanks de verbeterde overleving, colorectaal carcinoom verantwoordelijk gebleven voor een aanzienlijk deel van de kanker gerelateerde sterfgevallen per jaar. Per jaar komen in Nederland meer dan 5.000 mensen te overlijden aan de gevolgen van colorectaal carcinoom[1]. Verwacht wordt, dat vanwege het ouder worden van onze huidige populatie het voorkomen van colorectaal carcinoom de komende jaren verder zal toenemen. Deze factoren maken dat het colorectaal carcinoom naar alle waarschijnlijkheid een significant onderdeel zal blijven van de aan kanker gerelateerde zorguitgaven binnen de Nederlandse gezondheidszorg.

HOOFDSTUK 1

In de introductie van dit proefschrift wordt de ontwikkeling van de colorectale chirurgie vanaf de Faraonische tijd beschreven. Vooral gedurende de laatste honderd jaar hebben zich grote ontwikkelingen voorgedaan. Waar eerst de behandeling bestond uit enkel een invasieve en vaak invaliderende chirurgische ingreep, wordt nu veelal een geïndividualiseerde behandeling gegeven die bestaat uit meerdere onderdelen. Hierbij kan bijvoorbeeld voorafgaande aan chirurgie worden gekozen voor een behandeling met radiotherapie, al dan niet in combinatie met chemotherapie (neoadjuvante chemoradiotherapie). Deze zogenaamde voorbehandeling beoogt de tumor te doen slinken of zelfs volledig

te doen verdwijnen wat kan resulteren in een beduidend minder invasieve/ invaliderende chirurgische ingreep. In sommige gevallen kan zelfs sprake zijn van het volledig verdwijnen van kwaadaardige cellen na chemoradiotherapie (complete respons) en kan dan worden afgezien van een chirurgische ingreep. Voorop staat hierbij dat de patiënt intensief wordt vervolgd met behulp van periodieke onderzoeken zodat een eventuele terugkeer van ziekte in een vroeg stadium kan worden opgespoord. Naast deze ontwikkeling bestaat de trend tot het behandelen van oppervlakkig gelegen relatief kleine tumoren met behulp van een zogenaamde lokale excisie. Bij deze behandeling wordt endoscopisch via de anus de tumor geëxcideerd (Transanal Endoscopic Microsurgery (TEM)).

Alle voornoemde behandelingen gaan gepaard met hun eigen, specifieke voor- en nadelen. De kans op een potentieel voordeel (bijvoorbeeld: een complete respons na chemoradiotherapie) of nadeel (bijvoorbeeld: het ontstaan van potentieel levensbedreigende complicatie na chirurgische ingreep) verschilt per patiënt en is multifactorieel bepaald. Daarnaast hecht ieder mens een andere waarde aan een bepaalde uitkomst. Bijvoorbeeld; voor de één kan het leven met een stoma een acceptabele situatie zijn, terwijl voor een ander deze uitkomst totaal onacceptabel is. Bovenstaande aspecten maken dat besluitvorming rondom colorectaal carcinoom een complex proces is, waarbij onder andere de voorkeuren en de kwetsbaarheid van de patiënt een belangrijke rol spelen. Een individueel gemaakte inschatting van behandeling gerelateerde risico's kan helpen om een goede afweging te maken tussen potentiële behandelingsstrategieën. Het doel van dit proefschrift is het definiëren van voorspellers/risico factoren voor klinisch relevante gebeurtenissen die kunnen helpen bij het bepalen van de behandeling en/of verrichten van aanvullende diagnostiek.

HOOFDSTUK 2

In dit hoofdstuk worden de opzet en de resultaten van een onderzoek naar mogelijke voorspellers van een complete response op chemoradiotherapie beschreven. Het onderzoek werd uitgevoerd op basis van patiëntgegevens die werden verkregen vanuit een landelijke database (DCRA database). Uit deze database werden alle 6.444 patiënten geselecteerd die tussen 2009 en

2016 chemoradiotherapie ondergingen voorafgaande aan een chirurgische resectie van een rectumcarcinoom. Bij 1.010 patiënten kon na chirurgische resectie geen vitale tumorcellen worden aangetoond door de patholoog in het resectiepreparaat. Dit werd beschouwd als een complete response op de chemoradiotherapie. Vervolgens werd een aantal, voorafgaande aan het onderzoek gedefinieerde, mogelijke voorspellers voor complete respons geanalyseerd in deze groep. Tumor stadium (relatief grote tumoren voorafgaande aan behandeling), aanwezigheid van lymfeklier metastasen, aanwezigheid van metastasen op afstand en tekenen van obstructie bleken de kans op complete respons onafhankelijk van elkaar evident te verkleinen. De beste respons op chemoradiotherapie werd gezien onder patiënten met een niet obstruerend goed gedifferentieerd adenocarcinoom laag (dicht bij de anus) in het rectum gesitueerd, zonder aanwijzingen voor metastasen op afstand. De kans op complete respons werd verder vergroot indien de resectie werd uitgevoerd tussen de 16 en 24 weken na chemoradiotherapie.

HOOFDSTUK 3

Na het in kaart brengen van de voorspellers voor complete respons werd een onderzoek gedaan naar de relatie tussen complete respons en het optreden van postoperatieve complicaties. De onderliggende hypothese was dat patiënten met een complete respons relatief veel ontstekingsreactie en verlittekening vertonen in de tumor-regio vergeleken met patiënten die geen volledige respons vertonen. Deze intensieve lokale reactie op de chemoradiotherapie zou vervolgens de operatie en hierop volgende genezing kunnen bemoeilijken, wat zou kunnen resulteren in een hoger percentage chirurgische complicaties bij patiënten met een volledig respons. Dit onderzoek werd uitgevoerd in een onderzoekspopulatie die eveneens werd verkregen uit de DCRA database. Resultaten van deze studie staan beschreven in hoofdstuk 3. Deze landelijke studie omvatte gegevens van 8.003 patiënten die tussen 2009 en 2017 werden behandeld met radiochemotherapie voorafgaande aan resectie van de tumor. De dataset werd gesplitst in patiënten die resectie met aanleggen van een anastomose (N=3.472) ondergingen en patiënten waarbij geen anastomose werd aangelegd (patiënten die dus een permanent stoma kregen, N=4.531). Dit werd gedaan omdat één van de uitkomstmaten, het optreden van lekkage van

de naad, per definitie uitsluitend voorkomt bij patiënten bij wie een anastomose is aangelegd. In deze groep werd gevonden dat lekkage van de naad frequenter optrad bij patiënten met een complete respons vergeleken met patiënten zonder complete respons (***odds ratio***: 1,49; 95% betrouwbaarheidsinterval: 1,04-2,15). Daarnaast werden frequenter chirurgische complicaties in zijn algemeenheid geobserveerd in de complete responsgroep (***odds ratio***: 1,56; 95% betrouwbaarheidsinterval: 1,25-1,95). In de groep patiënten waarbij primair een stoma was aangelegd werden geen significante verschillen gevonden in het voorkomen van chirurgische complicaties tussen patiënten met of zonder complete respons. Op basis van bovenstaande resultaten concludeerden wij dat bij patiënten bij wie na chemoradiotherapie een naad is aangelegd, het beloop relatief frequenter wordt gecompliceerd door een lekkage van de naad of andere chirurgische complicaties, indien sprake is van een complete respons in het gereseceerde preparaat.

HOOFDSTUK 4

In dit hoofdstuk worden de ontwikkeling en validatie beschreven van een predictie model voor het voorspellen van postoperatief overlijden na colorectale chirurgie. Het model werd ontwikkeld op basis van gegevens die werden verzameld in het Zaans Medisch Centrum bij patiënten die colorectale chirurgie ondergingen in de periode tussen 1990 en 2005. Op basis van deze gegevens werd een logistisch regressie model gemaakt waaruit vervolgens een gesimplificeerde risico score werd ontwikkeld. Vervolgens werd het model extern gevalideerd in groep patiënten die colorectale chirurgie ondergingen in Universitair Ziekenhuis Vall d'Hebron te Barcelona, Spanje tussen 2005 en 2011. De sterkste onafhankelijke predictoren voor mortaliteit die werden geïdentificeerd waren; tumor stadium (***odds ratio***: 3,2; 95% betrouwbaarheidsinterval: 2,8-4,6), leeftijd (***odds ratio***: 13,1; 95% betrouwbaarheidsinterval: 6,6-26,0), respiratoir falen (odds ratio: 4,9; 95% betrouwbaarheidsinterval: 3,3 – 7,1), hartfalen (***odds ratio***: 3.7; 95% betrouwbaarheidsinterval: 2,6-5,3) en spoed colorectale chirurgie (***odds ratio***: 6,7; 95% betrouwbaarheidsinterval: 4,7-9,5). Deze voorspellers werden geïncludeerd in het gesimplificeerde scoringssysteem. Bij externe validatie liet het model een goed voorspellend vermogen zien voor postoperatieve mortaliteit na colorectale chirurgie (***area under the curve*** 0,83).

HOOFDSTUK 5

In deze studie werden mogelijke voorspellers voor het optreden van een delier na colorectale chirurgie onderzocht. Een delier is een voorbijgaande toestand van acute verwardheid die onder andere regelmatig wordt gezien na chirurgie. Het optreden van deze toestand is belastend voor patiënt en geassocieerd met onder andere het optreden van andere postoperatieve complicaties en een verlengde opnameduur. Er zijn verscheidene preventieve maatregelen beschreven die de kans op het optreden van een postoperatief delier lijken te verkleinen. Door het identificeren van risicofactoren (voorspellers) voor het optreden van een delier kunnen patiënten met een verhoogd risico hierop vroegtijdig worden geïdentificeerd. Het onderzoek werd uitgevoerd onder patiënten die tussen 2009 en 2012 colorectale chirurgie ondergingen in het Universitair Medisch Centrum Groningen. In deze periode werden 436 patiënten geïncludeerd in de onderzoekspopulatie. Bij 45 (10,3%) van deze patiënten werd gedurende het postoperatieve beloop een delier geobserveerd. Patiënten die een delier ontwikkelden hadden een grotere kans om tijdens de betreffende opname te overlijden (8,9% versus 3,6%, P-waarde: 0,09) en waren gemiddeld langer opgenomen in het ziekenhuis. Risicofactoren voor het optreden van een delier waren; een psychiatrisch ziektebeeld in de voorgeschiedenis (***odds ratio***: 8,4; 95% betrouwbaarheidsinterval: 1,5–46,8), leeftijd (***odds ratio***: 4,0; 95% betrouwbaarheidsinterval: 1,6–10,4) en bloedtransfusie rondom de operatie (***odds ratio***: 2,4; 95% betrouwbaarheidsinterval: 1,1–5,1).

HOOFDSTUK 6

Na een in opzet curatieve chirurgische resectie van een colorectaal carcinoom bestaat de kans op terugkeer van de ziekte. Dit kan zich lokaal voordoen (ter plaatse van het eerdere operatie gebied), of op een andere locatie zoals de long of de lever. In de meeste gevallen van terugkerende ziekte wordt dit gedurende de eerste jaren na operatie geobjectiveerd. In het geval van terugkerende ziekte kan het zinvol zijn een aanvullende (chirurgische) behandeling te starten. Dit kan, zeker indien terugkerende ziekte in een vroeg stadium wordt gediagnosticeerd, in een deel van de gevallen alsnog tot curatie leiden. Het is dan ook gebruikelijk om patiënten na colorectale chirurgie poliklinisch te volgen. Hierbij wordt periodiek aanvullend onderzoek verricht voor de detectie

van terugkerende ziekte. Één van de standaard methoden die hierbij wordt toegepast is het bepalen van de hoeveelheid CEA (carcinogenic embryonic antigeen) in het bloed. Deze zogenaamde tumor marker vertoont vaak verhoogde waarden indien sprake is van recidief ziekte. Helaas is de positief en negatief voorspellende waarde van deze marker beperkt. Hierdoor kan ten onrechte diagnostiek wordt ingezet (bij een positieve testuitslag terwijl geen sprake is van ziekte) of terugkerende ziekte wordt gemist (negatieve testuitslag bij terugkerende ziekte). In de studie, beschreven in hoofdstuk 6, onderzoeken wij de voorspellende waarde van het periodiek bepalen van een andere tumor marker te weten; tissue polypeptide antigen (TPA) gedurende de follow-up na resectie van een colorectale maligniteit. Hiervoor werden bij 572 patiënten uit 3 verschillende ziekenhuizen bloedserum samples verzameld en opgeslagen. Hieruit werden TPA waardes bepaald. De voorspellende waarde van periodiek bepaald TPA voor de detectie van recidief ziekte werd berekend op basis van de *area under the receiver operating characteristic curve*. Deze bleek 0,70 te zijn en komt overeen met een relatief gering voorspellend vermogen. Vergeleken met CEA zou 40% van de patiënten bij wie terugkerende ziekte was gedetecteerd met behulp van CEA-metingen zijn gemist bij het uitsluitend bepalen van TPA.

CONCLUSIE

Concluderend is het colorectaal carcinoom een frequent gediagnosticeerde vorm van kanker die ondanks de afname in mortaliteit nog steeds verantwoordelijk is voor een significant deel van de kanker gerelateerde sterfgevallen. De afgenomen mortaliteit is een gevolg van vele ontwikkelingen die zich de afgelopen decennia hebben voorgedaan. De behandeling is geëvolueerd van een ingrijpende hoog risico operatie tot een multimodale behandelingsstrategie waarbij de nadruk ligt op een individueel uitgezet behandelingstraject. Hierbij is het chirurgisch deel van de behandeling veiliger en veelal minder invasief geworden dankzij onder andere verbeterde chirurgische technieken en de introductie van neoadjuvante behandelingen. De voorkeur en kwetsbaarheid van de patiënt wordt de afgelopen decennia steeds meer meegenomen in het bepalen van de behandelingsstrategie. Om een weloverwogen behandel beslissing te nemen, is het belangrijk om naast de voorkeur van de patiënt

informatie te hebben over de daadwerkelijke kansen op bepaalde positieve danwel negatieve uitkomsten. In dit proefschrift wordt een aantal voorspellers van klinisch relevante gebeurtenissen in kaart gebracht.

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APPENDICES

LIST OF PUBLICATIONS

van der Sluis FJ, Couwenberg AM, de Bock GH, Intven MPW, Reerink O, van Leeuwen BL, van Westreenen HL. *Population-based study of morbidity risk associated with pathological complete response after chemoradiotherapy for rectal cancer.* Br J Surg. 2020 Jan;107(1):131-139.

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DANKWOORD

Het eerste artikel waarop dit proefschrift is gebaseerd werd gepubliceerd in 2014. Ten tijde van dit schrijven ruim 5 jaar geleden. Dit lijkt relatief kortgeleden echter het onderzoek waarop dit artikel is gebaseerd werd gestart 4 jaar daarvoor tijdens mijn ANIOS tijd in het Zaans Medisch Centrum. Terugkijkend ben ik 9 jaar bezig geweest met de inhoud van het voor u liggende proefschrift. Naast het onderzoek heb ik in deze periode de opleiding tot chirurg afgerond. Het was een drukke periode met de nodige hobbels voor mij en mijn omgeving. Graag wil ik hieronder mijn dank uitspreken voor een aantal bijzondere mensen die direct hebben geholpen bij het tot stand komen van mijn proefschrift en mensen zonder wiens steun het niet was gelukt.

Prof. dr. De Bock, Beste Truuske, via Barbara kwamen wij aan het begin van mijn opleiding in het UMCG in contact. Op dat moment had ik hulp nodig bij een aantal statistische aspecten van één van de artikelen waarop het proefschrift is gebaseerd. Van het één kwam het ander en inmiddels zijn we vijf publicaties verder. Onafhankelijk van of je nou tweede, vierde of laatste auteur was, heb je naar al deze studies/ artikelen met veel aandacht en oog voor detail gekeken. Je kwam met input die mij lieten zien dat je er aandacht en tijd in stak (tot aan de laatste letters van de conclusie). Als ik zelf dacht dat het “goed” was bleken er vaak toch nog wat puntjes op de i gezet te moeten worden. Ik ben ervan overtuigd dat dit voor al onze publicaties heeft geleid tot een kwalitatief goed resultaat. Oog voor detail en pas tevreden zijn als het echt goed is zijn kwaliteiten die ik zeer in je waardeer. Daarnaast is het je gelukt met succes mijn begeleider te zijn de afgelopen jaren. Ik kan me voorstellen dat het op tijden ‘lastig’ moet zijn geweest om met iemand te werken die naast onderzoek ook een drukke baan als chirurg in opleiding heeft en een gezinsleven. Toch ben je, je tijd in mij en mijn onderzoek blijven investeren. Veel dank daarvoor.

Prof. dr. Van Leeuwen, beste Barbara, ik ken je nu vanaf mijn ANIOS-tijd in het UMCG alwaar je mij (gelukkig) wist te motiveren mijn onderzoeksactiviteiten weer op te pakken. Dit heeft geresulteerd in een aantal mooie publicaties. Misschien heb je (net als ik) niet altijd 100% vertrouwen gehad in of er ooit

een proefschrift zou komen. In ieder geval, heb je mij gedurende de afgelopen jaren altijd gesteund, vertrouwen getoond en keuzes bij mij gelaten (zonder enige druk). De laatste jaren heb ik voor het grootste deel doorgebracht in de Isala Klinieken en heb daardoor helaas je begeleiding in persoon en lichtelijk sarcastisch getinte humor moeten missen. Met name het laatste ben ik onwijs gaan waarderen en missen. Veel dank voor al je hulp gedurende de afgelopen jaren.

Beste Erik, Na mijn aankomst in de Isala besloot ik dat het goed zou zijn een lokale coach te organiseren. Jouw enthousiasme en energie op zowel de ok als daarbuiten werkten aanstekelijk. Het was voor mij dan ook een logisch besluit om jou als co-promotor te vragen. Een besluit waar ik geen moment spijt van heb gehad. Je coaching op de ok en op het gebied van onderzoek hebben mij de afgelopen jaren gemotiveerd en vooruitgeholpen. Je bent een handige operateur en ik heb een aantal mooie trucjes van je mogen leren waar ik overigens nog dagelijks gebruik van maak. Veel dank daarvoor.

Dr. C Verberne, dr. A. Muller Kobold en prof. dr. Wiggers, dank voor de mogelijkheid om gebruik te mogen maken van de vele data en samples die jullie hebben verzameld. Dankzij deze data hebben we het onderzoek kunnen doen naar de waarde van TPA in het voorspellen van recidief colorectaal carcinoom (hoofdstuk 6). Het analyseren van deze data was complex en hiermee kom ik bij Zhuozhao Zhan; een statistische eindbaas zonder wie het niet gelukt zou zijn valide conclusies te trekken op basis van al die data.

Zhuozhao Zhan, dear Zhan, before starting on the statistics of the study presented in chapter 6, I was under the impression that I had some statistical skills. How wrong I was. Because of your help we were able to draw conclusions from the dataset. I am very thankful for your contribution and guidance in the statistical world. Thank you.

Dr. R. Pol en drs. M. Meerdink, beste Robert en Mark, dank voor jullie hulp met betrekking tot de studie beschreven in hoofdstuk 5. Mark; je hebt ongeloofelijk

veel tijd en energie gestoken in het verzamelen van alle data; chapeau! Dat hebben we maar mooi even 'gefikst'! Jij wist deze bal aan mij door te sturen zodat ik (bijna) een balletje voor open doel had. Robert; het was prettig met je samen werken; no nonsense, snelle reacties en een mooi artikel welke we in no time in een top blad wisten weg te zetten.

Alice Couwenberg en Martijn Intven, hartelijk dank voor de bereidheid tot samenwerking die jullie hebben getoond toen ik via het DICA contact met jullie opnam. Supermooi dat op deze wijze voor een ieder mooie resultaten zijn behaald! Naast het delen van data is door jullie ook inhoudelijk een significante bijdrage geleverd die mede heeft geleid tot de (naar mijn bescheiden mening) hoge kwaliteit van het in hoofdstuk 3 beschreven onderzoek.

Prof. dr. J.C. Haan, u heeft een waarlijke rol als mentor vervuld tijdens en ook na mijn studententijd. Uw steun en filosofisch getinte adviezen hebben altijd veel voor mij betekend. Vaak denk ik nog terug aan onze epische reizen gevuld met culturele hoogtepunten. Ondank het feit dat wij elkaar minder zijn gaan zien staat u in mijn achting nog steeds op éénzame hoogte.

Mijn paranimf, Joost van der Hart; gozer we hebben samen reeds vele mooie dingen meegemaakt. Vele hiervan waren samen met prof. dr. J.C. Haan. Ook nu weer ben jij getuige van een voor mij life eventje. Veel dank voor je tijd. Ik begrijp dat het inhoudelijk allemaal vrij saai moet zijn en des te meer weet ik je aanwezigheid te waarderen. Nog ff volhouden voor u het weet staan we aan de langgerekte statafel met goudenvochtkraan.

Marinus; reeds lang voor de eerste letter van dit onderzoek (of welk ander onderzoek van mij) ooit op papier kwam te staan was jij reeds overleden. Inhoudelijk heb je er nooit wat mee te maken gehad (behalve dan dat je eraan bent overleden). Maar net als mijn vader heb je invloed gehad op mijn mentale vorming en keuzes. Reeds op jonge leeftijd werden mijn hersens vol gepropt met ietwat militaristische ideeën over: "nooit opgeven", niet wijken en mannen

van stavast (nog steeds niet geheel erachter wat het laatste betekent). Ik mis je nog steeds.

Lieve pap en mam, zoals beschreven in de inleiding van dit dankwoord heb ik geruime tijd gedaan over de totstandkoming van mijn proefschrift. Het was bij tijden leuk (vooral de momenten waarop een artikel was geaccepteerd) maar soms ook minder leuk en tijdrovend. Ook al had ik reeds een opleidingsplek en besloten te differentiëren in de traumachirurgie, ik wilde op goede wijze afmaken waarmee ik was begonnen. Ik weet niet of het genen zijn of opvoeding, maar mentaliteit en doorzettingsvermogen zijn waarden die ik van jullie heb meegekregen (op welke wijze dan ook). Je maakt af waaraan je begint en ‘s avonds een vent ‘s ochtends een vent, kreeg ik frequent te horen (vooral op zaterdag ochtend). Deze mentaliteit heeft mij de afgelopen jaren op vele momenten geholpen en op mijn beurt hoop ik deze mee te geven aan jullie kleinkinderen (zijn inmiddels al minstens zo “volhardend” als wij samen in kwadraat). Ik ben trots om jullie zoon te zijn.

Mijn broer en paranimf, Marijn; je hebt ons de afgelopen jaren menig maal geholpen met verhuizen. De laatste verhuizing was naar Zwolle waardoor wij na jaren wederom in dezelfde stad zijn komen te wonen. Beste broer, jij bent een gozer waar ik van jongs of aan altijd op heb kunnen rekenen. Dank voor wie je bent, ik ben trots op je! Een aantal jaar geleden heb je een super leuke dame aan de haak geslagen (of andersom); Ilka. Mooi om te zien hoe je mijn broer gelukkig maakt. Ook extreem mooi dat (nu nog) kleine Indy erbij is gekomen. Veel dank voor je last minute hulp bij het maken van een door ieder goedgekeurde pasfoto ;).

Lieve Ariana en Alana, helaas gaat dit boekje niet over twee zusjes genaamd Elsa en Anna en een ijspaleis, ook Peppa pig komt er niet in voor. Ik weet het, heel saai maar het is zoals het is. Tegen de tijd dat jullie beide goed kunnen lezen en misschien de inhoud begrijpen, zullen we een aantal jaren verder zijn. De inhoud van dit boekje is tegen die tijd waarschijnlijk achterhaald en papier zal worden beschouwd als een nodeloos milieubelastend medium. Als ik jullie

was dan zou ik dus ook uitsluitend deze paragraaf lezen (niet verder vertellen maar de rest is saai). Misschien zullen jullie je kunnen herinneren dat ik me in de eerste jaren van jullie leven af en toe probeerde af te zonderen om te werken op mijn laptop (een opklapbare mobiele computer met een ouderwets toetsenbord) aan onderzoek. In het begin lukte dit vrij goed; Alana lag rustig te brabbelen onder mijn zoveelste bananenplant (deze planten gingen meestal binnen 6 maand dood, ben inmiddels gestopt ze te kopen, kan blijkbaar beter een half dooie patiënt in leven houden dan een f#ckin plant) terwijl ik zat te werken. Toen Ariana erbij kwam en jullie ouder werden, werd dit "afzonderen" steeds lastiger. Vaak kwam Ariana na een klein half uurtje 'helpen'. Zij kwam dan naast mij zitten en beloofde plechtig stil te zijn. Meestal na 1 minuut begon zij te vragen of het nog lang ging duren. Een vraag die zij vervolgens elke halve minuut herhaalde totdat ik met een zucht mijn laptop dichtklapte en besloot de geplande activiteit naar de avond te verplaatsen. Eigenlijk ging ik ook veel liever met Alana hardlopen (Alana dan op de fiets) of met jullie 'schilderen'. Vrij snel wisten jullie mij te leren dat als wij overdag samen waren, ik beter geen onderzoek of werk gerelateerde activiteiten kon plannen; dit bleek namelijk een absolute set up for failure. Veel dank voor deze les. Het heeft mijn leven de betreffende dagen een stuk leuker gemaakt. Ik ben, en zal altijd zijn, jullie grootste fan; papa.

Angelica, lieve lieve Angelica, in mijn leven ben ik 5 maal verliefd geworden. Drie van die keren waren gedurende mijn middelbare school tijd in Zwolle. De eerste liefde was jij, de tweede een elektrische gitaar (tot spijt van mijn ouders) en de derde een Honda SS50 (tot zorg van mijn ouders). De honda werd verkocht en de gitaar staat tegenwoordig vooral stof te happen. Maar jij bent de afgelopen 23 jaar vrijwel continu mijn liefde gebleven. In deze jaren heb je mij gesteund bij veel van wat ik deed of ondernam. Toen ik besloot te gaan werken in het UMCG en door de week ging wonen in Groningen heb je mij hierin gestimuleerd. Deze beslissing heeft een grote en negatieve impact gehad op ons privé leven en met name jouw professionele leven. Uiteindelijk gaf je je baan op en verhuisde vanuit het westen des lands naar het hoge noorden. Ze zeggen; er gaat niets boven Groningen. Daar was en ben jij het niet geheel mee eens geworden. Ondanks dit alles ben je mij altijd voor de volle 110 % blijven steunen. Zonder

deze steun was veel (waaronder dit proefschrift) niet gelukt. Naast al die steun vind ik het na 23 jaar nog steeds super om samen dingen te doen en nieuwe dingen/ skills te ontdekken.

En wat die andere 2 maal dat ik verliefd ben geworden betreft; daar ben jij ook verantwoordelijk voor. Ik ben je oneindig dankbaar voor onze twee fantastisch mooie meisjes. Dankjewel voor wie je bent. Ik hou van je.

CURRICULUM VITEA AUCTORIS

Frederik Jan van der Sluis werd op 9 mei 1981 geboren te Zwolle. Hij groeide op aan de kop van de Veluwe in het fraaie Hanzestadje Hattem. Na het behalen van zijn Atheneum diploma (op een paar zesjes na cum laude) aan het Carolus Clusius College te Zwolle, werd hij uitgenodigd voor de studie geneeskunde in Rotterdam. Alhier werden tal van levenslessen opgedaan en ontwikkelde hij een passie voor de mooiste specialisatie binnen de geneeskunde. Gedurende deze periode werden diverse buitenlandse 'stages' en onderzoeksprojecten ondernomen waaronder een analyse naar decompressie ziekte onder professionele duikers in de Golf van Mexico (onder begeleiding van prof. Cuauhtemoc Sanchez in samenwerking met Divers Alert Network South America) en een stage traumachirurgie in het universitaire ziekenhuis te Cairo (Ain Shams UMC). Na een milde vertraging werd in 2007 het artsexamen met goed gevolg afgelegd (wederom bijna cum laude). Kort hierop werd door hem eveneens een Master klinische epidemiologie afgerond. Een brede wetenschappelijke basis waar hij de afgelopen jaren veel profijt van heeft gehad.

Hierop werd door hem besloten dat de tijd was aangebroken om daadwerkelijk aan de slag te gaan als arts. In 2008 werd gestart als ANIOS heelkunde in het Reinier de Graaf gasthuis te Delft (prof. van der Elst). Na de eerste zes maanden te zijn doorgekomen bleek de heelkunde nog steeds datgene te zijn wat hem blij maakte. Na een intermezzo in het Zaans Medisch Centrum kwam Frederik Jan te werken in het Universitair Medisch Centrum te Groningen (opleider dr. van Ginkel), alwaar hij een opleidingsplek wist te bemachtigen. Na twee jaar academie wist hij te ontsnappen uit het UMCG en vervolgde zijn opleiding in de Isala klinieken te Zwolle (opleider dr. van Helden). Alhier wist hij zich ook de technische kneepjes van het vak meester te maken.

In 2017 begon hij met de differentiatie traumachirurgie in de Isala klinieken (opleider dr. Van Helden). Het laatste jaar van de differentiatie werd gevolgd in het Deventer ziekenhuis (onder begeleiding van dr. Roerdink en dr. Flikweert). Hier werd hij uiterst warm ontvangen en werden alle mogelijkheden geboden om zogenaamde 'vlieguren' te maken. Tevens maakte hij zich daar de scopische liesbreuk chirurgie meester (met dank aan dr. Bosker en dr. Talsma).

Gedurende zijn arts-assistentschap werden door hem diverse studies uitgevoerd, gepubliceerd en gepresenteerd op verschillende internationale congressen. Een aantal van deze studies staan beschreven in dit proefschrift.

In maart 2019 ontving Frederik Jan zijn registratie als traumachirurg. Sindsdien is hij werkzaam als fellow-traumachirurg in de Isala klinieken te Zwolle. In deze stad is hij momenteel woonachtig samen met zijn drie dames. In zijn vrije tijd kijkt hij netflix en werkte aan dit proefschrift...